UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

CEPHALON INC. and CIMA LABS, INC., Plaintiffs v. MYLAN PHARMACEUTICALS INC., and MYLAN INC. Defendants.	Civil Action No. 11-0164-SLR

MYLAN DEFENDANTS' RESPONSIVE POST-TRIAL BRIEF ON NON-INFRINGEMENT OF U.S. PATENTS 6,200,604, 6,974,590 AND 8,119,158

PRICKETT, JONES & ELLIOTT, P.A.

Elizabeth M. McGeever (No. 2057)
1310 King Street
P.O. Box 1328
Wilmington, DE 19899
(302) 888-6500

ROTHWELL FIGG ERNST & MANBECK, P.C.

E. Anthony Figg
Sharon L. Davis
C. Nichole Gifford
Seth E. Cockrum
Brett A. Postal
Rachel M. Echols
607 14th Street, N.W.
Suite 800
Washington, D.C. 20005
(202) 783-6040

Attorneys for Defendants-Counterclaim Plaintiffs Mylan Pharmaceuticals Inc. and Mylan Inc.

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I. NATURE AND STAGE OF THE PROCEEDINGS

The Court held a bench trial from March 11 through March 15 in this consolidated patent action. Plaintiffs, Cephalon, Inc. and Cima Labs (collectively "Cephalon" or "Plaintiffs"), filed their Opening Post-Trial Brief on Infringement on April 17, 2012. Defendants, Mylan Pharmaceuticals Inc. and Mylan Inc. (collectively "Mylan" or "Defendants"), submit this Responsive Post-Trial Brief on Non-Infringement setting forth the factual evidence and legal grounds in support of a judgment that the commercial manufacture, use, and sale of the generic fentanyl buccal tablets that are the subject of Mylan's Abbreviated New Drug Application ("ANDA") No. 202577 ("Mylan's ANDA product") will not directly infringe or induce infringement of the asserted claims of U.S. Patent Nos. 6,200,604 ("the '604 patent"), 6,974,590 ("the '590 patent"), and 8,119,158 ("the '158 patent").[1]

II. SUMMARY OF THE ARGUMENT

A. Mylan's ANDA Product Does Not Infringe the Asserted Claims of the '604 or '590 Patents (the "Khankari Patents")

The crux of the parties' dispute regarding infringement of the '604 and '590 patents is whether Mylan's ANDA product contains an "effervescent agent in an amount sufficient to increase absorption . . . across [the] oral mucosa," a limitation of each asserted claim. That term, as properly construed by the Court, means:

> at least one compound that evolves gas by means of an effervescent reaction is present in an amount sufficient to increase the rate and/or extent of absorption of an orally administrable medicament across the oral mucosa.

[1]Six patents were originally at issue in this litigation. Prior to trial, the parties substantially narrowed the asserted claims and defenses. At trial, Cephalon only asserted infringement of claims 1, 2, 3, 11 and 12 of the '604 patent, claims 1, 2 and 7 of the '590 patent, claims 1, 15, 17, 19 and 21 of the '158 patent, and claims 1, 3, 4 and 5 of the '92,832 patent. Mylan does not contest infringement of the '92,832 patent, but asserts that those claims are invalid. Mylan addressed the invalidity of the asserted claims of the '92,832 patent and the '158 patent in its Opening Post-Trial Brief on Invalidity.

> This amount is greater than that required for disintegration and does not include the pH-adjusting substance separately claimed.

See Cephalon, Inc. v. Watson Pharms., Inc., 769 F. Supp. 2d 729, 743 (D. Del. 2011).[2] The Court's construction was not appealed by either party in the prior Watson litigation, and the parties have agreed to that construction in this case. It requires proof that effervescence itself increases drug absorption and includes two important qualifications. First, the amount of effervescent agent that allegedly increases the absorption of fentanyl across the oral mucosa must be greater than the amount required for disintegration. In other words, the well-known prior art function of effervescence in aiding tablet disintegration was not part of Plaintiffs' invention and cannot be considered as part of the amount of effervescence that allegedly increases absorption.[3]

In its post-trial brief, Cephalon attempts to circumvent this requirement by arguing that none of the effervescence in Mylan's tablet is "required" for disintegration. *See* D.I. 153 at 2. But it is Cephalon's burden to prove the opposite, namely that the effervescence in Mylan's product increases absorption and does so beyond its effect on tablet disintegration. The evidence presented at trial showed that the only function of effervescence in Mylan's tablets is to achieve rapid tablet disintegration, which is an important feature for a tablet designed to deliver the drug rapidly to the

[2] The Khankari Patents were the subject of prior litigation between Cephalon and Watson in this Court. The Federal Circuit affirmed this Court's decision that the non-effervescent Watson ANDA product, which was bioequivalent to the Fentora® tablet, did not infringe. Although the Federal Circuit reversed the judgment that the Khankari Patents are invalid, it did so because Watson failed to meet its burden of proof on the enablement issue. *See Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1340 (Fed. Cir. 2013). Enablement is not an issue in this case.

[3] When construing this claim language, the Court determined, based on arguments Cephalon made to the Patent Office to distinguish its invention over the prior art, that the amount of effervescent agent used to increase drug absorption is distinct from the amount of effervescence used for disintegration and therefore must be greater than the amount of effervescence that serves the prior art function of tablet disintegration. *See Cephalon, Inc. v. Watson Pharms., Inc.*, 769 F. Supp. 2d at 745-746.

system circulation. Plaintiffs have failed to prove that effervescence has any effect on absorption beyond its well-known effect on tablet disintegration.

Second, the Court's claim construction requires that the amount of effervescence that is allegedly increasing absorption does not include the pH-adjusting substance separately claimed.[4] D.I. 150 at 789:2-6. The evidence presented at trial showed that the use of a pH adjusting substance to raise the pH in the mouth is important to ensure that fentanyl is in the absorbable unionized form. In its post-trial brief, Cephalon attempts to alter this requirement of the Court's construction by arguing that the effervescence acts "synergistically" with the pH modifier to affect absorption. Aside from the lack of evidence of such synergism, the Court has already rejected that argument. *Cephalon, Inc. v. Watson Pharms, Inc.*, 769 F. Supp. 2d at 745("The claims separately require at least one 'effervescent agent in an amount sufficient to increase absorption' and 'at least one pH adjusting substance.' While one compound may both adjust pH and participate in effervescence, only the quantity of effervescent agent above that needed for effervescence may be considered the 'pH adjusting substance.'"); *see also* Section III(c) below.

Thus, to prove infringement, Plaintiffs must prove that the Mylan ANDA product contains an amount of effervescence in excess of that required for rapid tablet disintegration and that such amount does not include the pH adjusting substance. Plaintiffs must prove that the effervescent agents themselves increase the absorption of fentanyl across the oral mucosa. Plaintiffs presented no evidence at trial that effervescence in Mylan's ANDA product enhances drug absorption other than by speeding the disintegration of the tablets.

In fact, Plaintiffs have never conducted a test to determine whether Mylan's ANDA product, or their own Fentora® product, contains an "effervescent agent in an amount effective to increase

[4]When construing this claim language, the Court determined that the amount of effervescent agent allegedly used to increase drug absorption is separate and distinct from the pH-adjusting substance. *See Cephalon, Inc. v. Watson Pharms., Inc.*, 769 F. Supp. 2d at 745-746.

absorption…across the oral mucosa." To assess the impact of effervescence on the rate and extent of fentanyl absorption *in vivo*, it would be necessary to compare two tablets, one having effervescence and one without effervescence, in which the other ingredients and characteristics (including disintegration rate and pH) are the same. Dr. Khankari was not aware of such a test, and Plaintiffs presented no evidence of such a test at trial. D.I. 147 at 218:12-220:4.

Plaintiffs attempted to convince the Court that effervescence improves drug absorption in two ways: (1) with unproven theories; and (2) by incorrectly interpreting certain experimental and clinical data. Although the Khankari Patents identify four theoretical mechanisms by which the inventors apparently believed that effervescence "may" act as a permeation enhancer to increase drug absorption (*see* JTX 2 at col. 2, ll. 15-27), Plaintiffs did not rely on those theories at trial. Rather, the so-called "dynamic pH" theory was the centerpiece of Plaintiffs' case. Plaintiffs' hypothesis is that effervescence produces the weak acid, carbonic acid, in the saliva, resulting in an initial drop in pH. According to Plaintiffs, this brief initial pH drop facilitates dissolution of fentanyl citrate. Plaintiffs' theory then requires that carbonic acid dissociate, forming gaseous carbon dioxide, which bubbles out of the saliva resulting in an increase in pH that converts ionized fentanyl to unionized fentanyl. D.I. 147 at 163:9-164:9; D.I. 153 at 9.

The evidence presented at trial revealed several fatal flaws in Plaintiffs' "dynamic pH" theory. First, Plaintiffs have never proven that an initial pH drop, followed by a subsequent rise (the so-called "dynamic pH"), actually happens when tablets are administered to patients. D.I. 150 at 795:4-16. It is undisputed that Plaintiffs never conducted any tests to determine if the pH shifts seen with *in vitro* testing actually occur when the tablets are administered to patients. Mylan presented undisputed testimony demonstrating that there are sound scientific reasons that effervescence cannot cause such pH shifts in the saliva in the mouth. *See* Section IV(B)(1)(d)(ii) below.

Second, Plaintiffs have failed to prove that the pH shifts observed in *in vitro* tests (and which Plaintiffs speculate occur in the mouth) are caused by effervescence. As Dr. Weiner explained without contradiction by Plaintiffs' experts, a more likely explanation for the pH shifts seen in the *in vitro* testing are the differences in solubilities of the acid and base components of the tablets. Specifically, as the more soluble citric acid component dissolves first, the pH drops, and as the less soluble carbonate bases then dissolve, the pH rises. *See* Section IV(B)(1)(d)(ii) below.

Third, Plaintiffs have provided no evidence that a dynamic pH shift, even if it occurred, would increase drug absorption across the oral mucosa. As Dr. Weiner explained, fentanyl citrate is water-soluble, and the amount of this potent drug that needs to be in solution is extremely small. Even in the highest dosage strength, the fentanyl citrate will completely dissolve in the amount of saliva present in the buccal cavity at the normal physiological pH of 7 or below. *See* Section IV(B)(1)(d)(ii) below. Furthermore, there is no basis to conclude that an extremely brief drop in pH (*i.e.*, during the first minute of a 30 minute administration period) could have any effect on the absorption of fentanyl. As Dr. Weiner explained, fentanyl does not have a memory, and it does not "know" whether it previously was at a pH that was higher or lower. The factors that are important to rapid absorption of fentanyl are rapid tablet disintegration and the inclusion of a pH adjusting substance that brings the pH to an optimal range in which fentanyl in the absorbable, unionized form is maximized. *See* Section IV(B)(3)(c) below.

Plaintiffs also rely on their incorrect interpretation of experimental and clinical data in an effort to convince the Court that effervescence increases absorption. Plaintiffs do so by consistently referring to formulations that contained both effervescence and a pH adjusting substance simply as "effervescent" formulations, without taking into account the effect that the pH adjusting substance

has on drug absorption in those formulations.[5] There can be no credible dispute that, consistent with the Court's claim construction, the Khankari patents describe the use of both "effervescence" and a "pH adjusting substance" as separate and distinct ingredients.[6] Yet, in the data presented at trial, including the results of the Ireland Study, the Anesta Study, the Absorption Systems Study, the Mylan buccal tablet development work (generic Fentora®), and the Mylan sublingual tablet development work (generic Abstral®),[7] all of the formulations labeled as "effervescent" contained both a pH adjusting substance and the components participating in the effervescent reaction.

In all of those studies, Plaintiffs improperly attribute any increase in drug absorption to effervescence and ignore the effect of the pH adjusting substance. However, it was well known prior to the filing of the Khankari Patents that the absorption of fentanyl is pH-dependent. It was also well known in the prior art that fentanyl is only absorbed to any appreciable extent in its soluble, unionized form, and that adding base to increase pH would convert fentanyl to its unionized

[5]Both Fentora® and the Mylan ANDA product contain citric acid, sodium bicarbonate and sodium carbonate in approximately the same amounts. In its New Drug Application ("NDA"), Cephalon identified the sodium bicarbonate and the citric acid as "effervescent components" and identified the sodium carbonate as "a pH adjustment component." *See* PTX 259 at CEP-FEN00029796.

[6]In the '604 patent, claim 1 includes an "effervescent agent in an amount sufficient to increase absorption . . . across the oral mucosa," but no pH adjusting substance. Claim 2 of the '604 patent adds the additional requirement of a separate "pH adjusting substance" as a dependent claim. The patent specification explains that "the present dosage forms may also include in amounts additional to that required for effervescence a pH adjusting substance." JTX 2 at col. 3, ll.14-16. The specification further states that "[s]uitable pH adjusting substance for use in the present invention include any weak acid or weak base in amounts additional to that required for the effervescence or, preferably, any buffer system that is not harmful to the mucosa…[or] any of the acids or bases previously mentioned as effervescent compounds. . . . " *Id*. at col. 3, ll. 44-51.

[7] Throughout their Opening brief, Plaintiffs mischaracterize statements from Mylan's development documents and take statements out of context to argue that Mylan "admitted" effervescence works to improve absorption. Plaintiffs are incorrect. As Dr. Wargo explained at trial, each and every time Mylan referred to "effervescence," Mylan was including all three components-citric acid, sodium carbonate and sodium bicarbonate. D.I. 148 at 431:3-8; 448:14-449:7. As a result, any characterization of "effervescence" in the Mylan documents necessarily included the effect of "effervescence" and the effect of the separate "pH adjusting substance." Furthermore, Dr. Wargo testified that Mylan never conducted any tests to determine whether effervescence increases the absorption of fentanyl across the oral mucosa. D.I. 148 at 507:12-24.

form. Therefore, in formulations containing both effervescence and a pH adjusting substance (excess base), any increase in drug absorption is attributable to the presence of the pH adjusting substance, not the effervescence -- a fact that Plaintiffs ignore.

Throughout the entire trial, the only scientific evidence involving testing of the effects of effervescence alone in a formulation that did not also contain a pH adjusting substance was the Absorption Systems Study. That study demonstrates that the pH adjusting substance increases absorption, while effervescence alone does not. The Absorption Systems Study included an *in vitro* permeability test comparing: (1) a formulation containing both effervescence and a pH adjusting substance; and (2) a formulation containing only effervescence without a pH adjusting substance, with all other ingredients being the same. The Absorption Systems Study also included a test formulation of fentanyl citrate dissolved in a solution. The results of the tests of these three formulations demonstrate that fentanyl with effervescence only (and no pH adjusting substance) provided approximately the same amount of drug absorption as a formulation that contained fentanyl citrate in a solution. In contrast, the formulation containing both effervescence and a pH modifier had much higher absorption than the formulation containing effervescence alone (without a pH adjusting substance). If effervescence (the bubbling of CO_2) increased fentanyl absorption, then the formula having effervescence only should have had better absorption than a non-effervescent fentanyl solution. D.I. 150 at 864:20-867:6. It did not. Therefore, as Dr. Weiner explained, one can conclude that it is the pH-adjusting substance, not effervescence, that causes any increase in drug absorption. The only role of effervescence in the Mylan ANDA product (and Fentora®) is simply its well-known prior art use of speeding tablet disintegration. Effervescence is not changing pH, and it is not increasing the rate or extent of drug absorption beyond any increase that is a result of faster tablet disintegration.

Plaintiffs argue that all of the "effervescent" formulations tested by Cephalon and Mylan showed better drug absorption than non-effervescent formulations. However, in every study on which Plaintiffs rely, formulations that were designated "effervescent" included both the effervescent agents and the basic pH adjusting substance. Plaintiffs made no effort to quantify, in any of those tests, the amount of drug absorption attributable to the pH adjusting substance, nor did they show that effervescence itself affects drug absorption. Therefore, none of the studies conducted by Plaintiffs or by Mylan provide any evidence that effervescence -- as opposed to the well-known effect of the pH adjusting substance -- increases the absorption of fentanyl across the oral mucosa. Additionally, the Absorption Systems data proves that it is the pH adjusting substance, not effervescence that is responsible for any increased drug absorption. The use of a pH adjusting substance alone, to increase drub absorption was well known in the prior art and is not Plaintiffs' invention. According to the Court's claim construction, the amount of effervescence that is increasing drug absorption must be separate and distinct from that of the pH adjusting substance. Because Plaintiffs have failed to prove that Mylan's ANDA product (or Fentora®) contains effervescent agents in an amount effective to increase absorption across the oral mucosa, Plaintiffs have not met their burden of proving infringement.

B. Mylan's ANDA Product Does Not Infringe the Asserted Claims of the '158 Patent

Mylan's ANDA product does not infringe the asserted claims of the '158 patent because it does not meet the claim limitation requiring the use of a non-effervescent pH adjusting substance. The asserted claims of the '158 patent contain a limitation requiring that the formulation include a "pH adjusting substance ***that is not a component of the effervescent material***." (emphasis added). As discussed in Mylan's claim construction briefing, this language means exactly what it says: the pH adjusting substance used must be a pH adjusting substance that is not part of the formulation's

effervescent material.[8] Because it is undisputed that sodium carbonate, a base that is used as a pH adjusting substance in the Mylan ANDA product, is an effervescent material and participates in the effervescent reaction that results from the use of that product (*see* D.I. 149 at 598:10-22, 611:14-17), Mylan's ANDA product does not infringe the asserted claims of the '158 patent.

III. COUNTERSTATEMENT OF FACTS

A. Plaintiffs Did Not Invent Fentanyl or the Use of Fentanyl for the Treatment of Breakthrough Cancer Pain

Plaintiffs did not invent fentanyl, the active drug substance in Fentora® and in Mylan's ANDA Product, and Plaintiffs did not invent the use of fentanyl for the treatment of cancer pain. D.I. 147 at 73:4-10. Fentanyl has been used for the treatment of chronic cancer pain since at least the early 1990s when Duragesic®, a fentanyl transdermal patch was approved. DTX 502 at 203. Prior to Cephalon's work on Fentora®, it was already well known that fentanyl was ideally suited for administration across the oral mucosa, because it is highly potent and is lipophilic. D.I. 147 at 73:24-74:9. It was also well known before 1998 that delivery of drugs across the oral mucosa was beneficial, because it avoids first pass metabolism in the liver. D.I. 147 at 157:8-24.

Plaintiffs also did not invent the oral transmucosal delivery of fentanyl or the use of fentanyl for breakthrough cancer pain. D.I. 147 at 73:4-10. In 1998, Anesta introduced Actiq®, an oral tranmucosal fentanyl citrate lozenge on a stick for the treatment of breakthrough cancer pain in patients already taking opioids around the clock for chronic cancer pain. D.I. 147 at 73:4-10. Actiq® became a Cephalon product when Cephalon acquired Anesta in 2000 and Plaintiffs

[8] The common specification of the Moe patents describe both effervescent and non-effervesent pH adjusting substances (*e.g.*, sodium carbonate and phosphate salts, respectively). JTX 6 at col. 27, ll. 29-32. While other of the Moe patents are directed to the use of a carbonate (*i.e.* effervescent) pH adjusting substance or are broad enough to include any pH adjusting substance, the claims of the '158 patent are directed to the embodiment that employs a non-effervescent pH adjusting substance.

implemented a plan to switch patients from Actiq® to Fentora®. PTX 411 at CEP-FEN 01389594; 01389671-72.

B. Plaintiffs Did Not Invent Effervescence or the Use of Effervescence As A Tablet Disintegrant

Plaintiffs can hardly dispute that effervescence is an excellent disintegrant. In fact, when Cephalon submitted its New Drug Application ("NDA") to the FDA, it told the FDA that the release of carbon dioxide from the effervescent reaction "facilitates disintegration of the tablet." D.I. 149 at 644:1-19; PTX 259 at CEP-FEN00029795. Indeed, Cephalon described the functions of the effervescent agents to the FDA as the "[acid or basic] component of [the] effervescent couple used to facilitate oral disintegration of the tablets." PTX 259 at CEP-FEN00029796

The use of effervescence to speed tablet disintegration was very well known prior to the March 1998 effective filing date of the Khankari patents.[9] D.I. 147 at 191:13-17; D.I. 150 at 793:12-19; DTX 413. In fact, the specification of the Khankari Patents recognizes that "effervescents have been employed to obtain rapid dissolution and/or dispersion of the medicament in the oral cavity," and cites several prior art disclosures to that effect. JTX 2 at Col. 1, ll. 38-40. Other prior art references describing the use of effervescence as a disintegrant were also cited during prosecution of the Khankari patents. JTX 3; JTX 5.[10]

[9] U.S. Patent No. 5,223,264 issued June 29, 1993, and teaches that effervescence can be used to rapidly disintegrate a tablet in the human mouth. D.I. 150 at 794:11-20; DTX 413 at col. 2, ll. 52-58. A person of ordinary skill in the art reading the '264 patent would have understood that the amount of effervescent agent sufficient to disintegrate a tablet is between 5-50% by weight of the final tablet composition. D.I. 150 at 794:21-25; DTX 413 at col. 5, ll. 59-64. By comparison, Example 1 of the Khankari Patents describes an effervescent fentanyl buccal tablet containing 36% effervescence. D.I. 150 at 795:1-3; JTX 2, col. 5, ll. 60-col. 6, ll. 30.

[10] During prosecution, the examiner rejected several of the claims in the Plaintiffs' application based on a prior art patent that disclosed the use of effervescence as a disintegrant. D.I. 150 at 791:15-792:3; JTX 3 at CEP-FEN00470269. To overcome that rejection, Plaintiffs were forced to amend their claims and argued to the Patent Office that their "invention" was not the use of effervescence as a disintegrant, but rather, the use of effervescence in an amount that is greater than

It was also well known prior to Plaintiffs' alleged invention that the absorption of fentanyl is pH dependent, and that the unionized form of fentanyl is the only form that is absorbed. D.I. 149 at 638:21-639:22, 656:8-10. At trial, Dr. Khankari agreed that prior to the development of the subject matter of his patents, it was known that adding base (a pH-adjusting substance) could be used to increase the saliva pH, which would convert fentanyl to the absorbable unionized form. D.I. 147 at 211:5-21; 162:22-24. In developing its fentanyl buccal tablet, Mylan employed these prior art principles.

C. Plaintiffs' Infringement Arguments Rely on An Improper Reading of the Court's Claim Construction

Each and every claim asserted against Mylan requires the presence of "at least one [saliva activated] effervescent agent in an amount sufficient to increase absorption . . . across the oral mucosa." As discussed above, this Court has construed that term in the prior Watson case, and the parties have agreed on that construction in this case.

Cephalon attempts to avoid the consequences of this claim construction by arguing that effervescence acts "synergistically" with the pH modifier to affect absorption and that effervescence may or may not aid in tablet disintegration. D.I. 153 at 2-4 and 31-34. Plaintiffs' arguments are inconsistent with statements Plaintiffs made during patent prosecution to distinguish its alleged invention over prior art and are also contrary to the Court's rationale for the claim construction. Moreover, Plaintiffs' "synergism" argument lacks evidentiary support and avoids the central issue, namely, that Plaintiffs have failed to prove that effervescence increases fentanyl absorption.

When construing this language in the claims, the Court determined, based on arguments Cephalon made to the Patent Office during prosecution to distinguish its invention over the prior art, that the amount of effervescent agent used to increase drug absorption is distinct from (and

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that necessary for disintegration in order to increase the rate and/or extent of absorption. D.I. 150 at 791:10-792:3.

therefore must be greater than) the amount of effervescence used for disintegration. *See Cephalon, Inc. v. Watson Pharms., Inc.*, 769 F. Supp. 2d at 745-746. The Court reasoned that that:

> The applicants argued, *inter alia*, that '[i]t is only the present invention that teaches that the amount of effervescent couple **should be** greater than that required for disintegration in order to achieve an improvement in transport of the active ingredient across the oral mucosa.' . . . In further acknowledgment of the difference between effervescents and disintegrants, the Khankari patents' specification states that 'effervescents have been employed to obtain rapid dissolution and/or dispersion of the medicament in the oral cavity' but, '[d]espite these and other efforts toward increasing the permeation of medicaments across the oral mucosa, there have been unmet needs for improved methods of administering medicaments across the oral mucosa' until the present invention. Thus, although the 'effervescent couple in combination with the other ingredients' will 'improve the disintegration profile' of the dosage form, and while a certain (surplus) amount of effervescents will also confer pH-adjusting benefits to the formulation, Watson is correct that these are distinct ingredients.

See Id. at 745-746 (emphasis in original)(internal citations omitted). The Court further cited statements made by Plaintiffs during prosecution of the '693 application (a continuation application which shares the same specification as the Khankari patents) in which Plaintiffs explained that:

> To further accentuate the differences between the present invention and the prior art, applicants have amended claim 22 to make it clear that in **the invention, a saliva activated effervescent couple is present in an amount that is greater than the amount necessary for tablet disintegration**. Indeed, the amount of saliva activated effervescent disintegration couple present must be sufficient to increase either the rate or the extent of absorption of the medication across the oral mucosa. Applicants have found that effervescents can be used for far more than merely allowing for disintegration of the tablet. While rapid disintegration exposes the drug such that it may be used by the body, unless an effervescent couple is present in sufficient amounts, amounts greater than that necessary for disintegration, it does not significantly participate in the drug absorption process. By providing effervescents in an amount that is greater than that necessary for achieving disintegration of the dosage form, it is possible to obtain these benefits.

See Id. at 742 (internal citations omitted)(emphasis added).

Plaintiffs distinguished their invention from the prior art by claiming that effervescence served a "new use" in their invention, namely, increasing drug absorption. *Id*. Plaintiffs clearly

told the patent examiner that the effervescent agents used for disintegration do not participate in the increased drug absorption. *Id*. After considering the statements in the patent specification and arguments that Plaintiffs made during patent prosecution, this Court correctly construed the claim to require that the amount of effervescence that is allegedly increasing absorption is greater than the amount required for disintegration.

During claim construction, the Court also specifically determined that the amount of effervescent agent used to increase drug absorption is distinct from the pH modifier, and expressly construed the claim to require that the amount of effervescence that is alleged to increase absorption does not include the pH modifier that is separately claimed. *See Cephalon, Inc. v. Watson Pharms., Inc.*, 769 F. Supp. 2d at 745-746. As the Court explained:

> The court is next tasked with determining the nature of the 'effervescent agent' of the invention. Watson argues all pH adjusting substances present in the tablet cannot be subsumed by the 'effervescent agent' limitation or the related requirement that the effervescent agent be present 'in an amount sufficient to increase absorption' across the oral mucosa. Cephalon admits that the concepts of effervescence and pH-adjustment are different, but [argues] that one component . . . can perform both functions. While both parties agree that the 'amount [of effervescent agent] sufficient to increase absorption' requires the 'rate and/or extent' of absorption to be increased, Watson argues that the amount of effervescent agent must be greater than that required for tablet disintegration. The court agrees with Watson's position….[T]he inventors distinguished the effervescent agent(s) from the other ingredients of the composition. The claims separately require at least one 'effervescent agent in an amount sufficient to increase absorption' and 'at least one pH-adjusting substance.' While one compound may both adjust pH and participate in effervescence, **only the quantity of effervescent agent above that needed for effervescence may be considered the 'pH adjusting substance.'**

Id. (emphasis added).

The Khankari Patents claim and describe "effervescence in an amount effective to increase absorption" separately from the "pH-modifier."[11] Additionally, during prosecution of the '590

[11] *See* Footnote 6, *supra.*

patent, Cephalon distinguished the invention of the Khankari Patents over the prior art by arguing that its invention required both an effervescent couple and a pH-adjusting substance, whereas the prior art (Robinson) did not claim a pH-adjusting substance "**as a separate agent**." *Id.* (emphasis in opinion).

During prosecution of the '604 patent, Plaintiffs amended the claims to add the limitation of "at least one effervescent agent in an amount sufficient to increase absorption . . . across the oral mucosa" to overcome anticipation and obviousness rejections based on the prior art Wehling reference. *Id.* at 738. In remarks about the amendment, Plaintiffs argued that "the present invention is directed to the use of effervescent agents ***alone or in combination with*** pH adjusting substances to promote the absorption of medicaments across the oral mucosa." *Id*. (emphasis added). Not only did Plaintiffs claim the amount of effervescent agent needed to increase absorption separately from the pH-adjusting substance, but during prosecution, the Plaintiffs argued that effervescence alone would promote absorption, without the use of any pH-adjusting substance. *Id.* at 742. Therefore, the amount of effervescence that is allegedly effective to increase drug absorption cannot include or rely on any effects of the pH-adjusting substance, and Plaintiffs' argument that it may rely on the "synergistic effects" of a pH-adjusting substance and effervescence to increase absorption across the oral mucosa must fail. To prove infringement, Plaintiffs must show the Mylan ANDA product contains an amount of effervescence, above and beyond that which is acting to speed tablet disintegration and that does not include the pH-adjusting substance. This amount must be proved to increase in the absorption of fentanyl across the oral mucosa. Plaintiffs have failed to carry their burden of proof. The argument that effervescence, independent of its effect on disintegration and independent of the separate effect of the pH-adjusting substance, increases fentanyl absorption is not only not supported by the evidence, it is contrary to well-established scientific principles and experimental evidence.

D. Mylan's Development Work

Mylan is a global pharmaceutical company with an emphasis on generic drug development. D.I. 148 at 449:25-450:2. When Mylan begins developing any generic drug, one of its first steps is a product literature search. D.I. 148 at 398:24-399:4, 453:10-14. The purpose of the literature search is to obtain information to describe the brand product in Mylan's ANDA (an FDA requirement) and to identify information in the public domain about the dosage form and the drug substance. D.I. 148 at 453:10-454:2. Mylan's fentanyl buccal project was no exception. D.I. 148 at 454:3-6.

For each development project, Mylan typically utilizes PowerPoint presentations at meetings to provide background information about the project and to track the history of the product development. D.I. 148 at 455:3-20. These presentations are also used to aid in preparing documents for FDA submission. *Id.* The presentations are updated over the course of the project, but once a slide is created, it remains in the presentation. *Id.*

The lead formulator on the fentanyl buccal tablet project was Ms. Tammy Bartley. D.I. 148 at 451:18-22. She had considerable formulation experience, but prior to her work on Mylan's ANDA product, she had never worked with an oral transmucosal formulation or an effervescent formulation. D.I. 148 at 384:9-17. After conducting a review of the published literature, Ms. Bartley prepared a presentation summarizing the information available in the public literature about Fentora®. D.I. 148 at 456:2-3; DTX 27. One of the slides in the presentation included information taken from a 2008 article published by Dr. Pather, a named inventor on the Khankari Patents, summarizing the so-called "dynamic pH" theory. DTX 27 at MYLAN 487571. Plaintiffs base a large part of their case on the argument that Mylan has "admitted" that "Fentora tablets use effervescence to cause a decrease in pH upon formation of carbonic acid and then a subsequent rise in pH as carbon dioxide is released from saliva in order to enhance absorption." D.I. 153 at 29.

Plaintiffs' heavy reliance on these so-called admissions is misplaced. Ms. Bartley testified at trial (by deposition) that she had "quoted" the information describing the "dynamic pH" theory from the Pather article. D.I. 148 at 389:16-390:18. Dr. Wargo also confirmed that Mylan did not independently evaluate or test the scientific principles reported in the Pather paper to determine their accuracy, but rather Mylan's formulators just "regurgitated" the theory from the published literature.[12] D.I. 148 at 457:2-7; D.I. 507:12–24. As Dr. Weiner testified, to the extent that Mylan's documents describe Dr. Pather's dynamic pH theory, they are wrong. D.I. 150 at 858:11-22.

Ms. Bartley's presentation also identified other literature references explaining that the absorption of fentanyl is pH-dependent. DTX 27 at 487576. Based on that information from the prior art, Mylan believed that with the right pH modification it could develop a non-effervescent tablet that was bioequivalent to Fentora®.[13] D.I. 148 at 404:14-17, 483:2-8.

The first three scale-up formulations that Mylan prepared and tested, Lots 306, 367 and 368 were non-effervescent. D.I. 148 at 405:10-13. The first batch, Lot 306, contained *inter alia*, fentanyl (fine grade), ascorbic acid and magnesium oxide (pH modifiers), sodium starch glycolate (disintegrant), and sorbitol (a filler). DTX 755 at MYLAN 479068; DTX 680 at MYLAN 518089. Mylan Lot 306 exhibited an *in vitro* pH profile that had an initial drop, followed by a gradual rise. DTX 680 at MYLAN 518086 (pH profile for Lot 306 - yellow circles). Thus, this non-effervescent formulation exhibited the same type of "dynamic pH" that Plaintiffs attribute to effervescence.[14] Effervescence could not have been responsible for the *in vitro* "dynamic pH" profile seen in Lot

[12]Indeed, the same statements from Ms. Bartley's presentation about the Pather article were subsequently incorporated, almost verbatim, into a presentation prepared by Dr. Danny Kuntz summarizing his own review of the fentanyl buccal project when he began working on the development of a generic version of Abstral®, a fentanyl sublingual tablet. D.I. 148 at 488:7-490:6.

[13]As the court is aware, another generic company, Watson Pharmaceuticals, Inc. developed a generic fentanyl buccal tablet that is bioequivalent to Fentora® but is not effervescent. *Cephalon, Inc. v. Watson Pharms., Inc.*, 769 F. Supp. 2d at 747-751.

[14] The pH profile for Lot 306 not only has an immediate drop in pH, but it has a much more gradual rise in pH when compared to Fentora® pH increase. D.I. 150 at 847:6-848:5.

306, as Plaintiffs claim is the case with Fentora®, because Lot 306 was not effervescent. Rather, as both Dr. Wargo and Dr. Wiener explained, the pH of Lot 306 drops to 4 immediately after the tablet is placed in solution because ascorbic acid is very soluble and will dissolve into solution quickly.[15] D.I. 148 at 508:5-509:15; D.I. 150 at 844:17-848:1. Then, the pH slowly rises to 9 because the magnesium oxide (a poorly soluble base) dissolves slowly.[16] *Id.* However, despite its "dynamic pH," Lot 306 did not provide good absorption when tested *in vivo*, and it was not bioequivalent to Fentora®. If Plaintiffs' "dynamic pH" theory were scientifically correct, then one would have expected the Lot 306 formulation to exhibit even greater pharmacokinetic availability when compared to Fentora®. D.I. 150 at 847:6-848:5. In fact, the poor absorption seen with Lot 306 was due to the fact that the pH is only in the "optimal range" for fentanyl absorption for a short period of time. D.I. 148 at 508:5-509:22; D.I. 150 at 845:11-23.

The next two scale-up batches Mylan tested, Lots 367 and 368 contained, *inter alia*, fentanyl (fine grade), dibasic sodium phosphate and potassium phosphate monobasic (pH modifiers), sodium starch glycolate (disintegrant) and mannitol (a filler). D.I. 148 at 471:1-472:11; PTX 48 at Table 1; PTX 49 at Table 1. The primary differences between Lot 367 and Lot 368 were the amounts of the pH modifiers included, because Mylan was targeting a pH of 7 for Lot 367 and a pH of 7.5 for Lot 368. *Id.* The *in vivo* pharmacokinetic data for lots 367 and 368 showed better absorption than Lot

[15] Dr. Weiner also confirmed that the initial drop in pH for Lot 306 is attributed to the dissolution of the ascorbic acid, just as the initial drop in Fentora® is due to the dissolution of citric acid. D.I. 150 at 846:14-847:5.

[16] The gradual increase in pH for Lot 306 is due to the gradual dissolution of magnesium oxide, just as the increase in pH for Fentora® is due to the dissolution of the bicarbonate and carbonate salts. D.I. 148 at 508:5-509:15; D.I. 150 at 844:17-848:1. The increase in pH for Lot 306 is more gradual as compared to Fentora® because magnesium oxide is not very soluble in an aqueous solution, and so it goes into solution much slower. *Id.*

306, but neither lot was bioequivalent to Fentora®.[17] D.I. 148 at 419:10-423:12, 472:12-473:9; PTX 50. The problem with Lots 367 and 368 was that the tablets disintegrated too slowly. D.I. 148 at 481:13-20.

The results of Mylan's *in vivo* dissolution testing showed that not a single one of the tablets from Lots 367 and 368 had disintegrated at the end of the 30-minute administration period. D.I. 148 at 476:6-477:2; DTX 680 at MYLAN 518160. The study protocol for Mylan's clinical trials instructed that if undissolved tablet remained in the subject's mouth after 30 minutes, the subject was to swallow the tablet with a glass of water. D.I. 148 at 468:14-470:18; DTX 547 at MYLAN 095424 and DTX 549 at MYLAN 499059. Because the *in vivo* disintegration study terminated at 30 minutes, it is impossible to know how long it would have taken the tablets containing only sodium starch glycolate and no effervescence to disintegrate in the mouth.[18] *Id.*; D.I. 150 at 850:9-12. Contrary to the Plaintiffs' assertion (D.I. 153 at 25-27, 44-46), the results from Mylan Lots 367 and 368 plainly show that the sodium starch glycolate alone in these tablets was insufficient to achieve complete tablet disintegration within the targeted administration time. By comparison, the *in vivo* disintegration data for the Fentora® tablets in these same studies indicate that some Fentora® tablets had disintegrated as quickly as five minutes, with an average disintegration time of 25.5 minutes.[19] DTX 680 at MYLAN 518160. In fact, in every biostudy Mylan conducted the average Fentora® *in vivo* disintegration time was under 30 minutes. *Id.*

[17]Lot 368 was almost bioequivalent to Fentora®. In fact, if Mylan were filing an NDA rather than an ANDA, Lot 368 would have been suitable for additional, independent studies to determine if it would be a viable drug product. D.I. 148 at 471:1-473:21.

[18]Dr. Illum agrees that it cannot be determined how long it would have taken Lot 367 and 368 to disintegrate completely. D.I. 149 at 684:6-25. However, given that none of the Lot 367 or 368 tablets dissolved in the allotted 30 minutes, but some of the Fentora® tablets did, it is readily apparent that the rate of disintegration for the Lot 367 and 368 tablets is slower than the rate of disintegration for the Fentora® tablets. D.I. 150 at 850:17-851:12.

[19]Plaintiffs point to specific instances in which patients taking Fentora® reported that remnants of the tablet also had to be swallowed. D.I. 153 at 25-26. However, there is a stark contrast between

To understand better the disintegration problems with Lots 367 and 368, Mylan undertook additional *in vitro* disintegration studies.[20] D.I. 148 at 478:10-481:6. The results of these studies showed that while the Fentora® tablet immediately disintegrated and dispersed within the first minute of exposure to aqueous media, the Mylan tablet remained intact and did not disintegrate even after 20 minutes. D.I. 148 at 478:10-480:20; DTX 32 at MYLAN 026040. The fact that Lots 367 and 368, which contained 5% sodium starch glycolate, a "super-disintegrant," remained substantially intact after 20 minutes, while Fentora® disintegrated during the first minute of these tests, refutes Plaintiffs' argument that "none" of the effervescence in Mylan's ANDA tablet is required for disintegration. Thus, Mylan established through both *in vivo* and *in vitro* results, that the effervescence in its tablets is required to achieve rapid tablet disintegration that is important for these tablets.

Mylan attributed Fentora®'s rapid disintegration to the effervescence, which through the formation of bubbles, causes rapid mechanical erosion of the tablet. D.I. 148 at 481:21-482:2. Plaintiffs argue that, because of the presence of sodium starch glycolate, no effervescence is required for disintegration. However, what is important for the rapid delivery of fentanyl across the oral mucosa is not only that the tablet disintegrates, but that it disintegrates during the period of

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the disintegration of the Fentora® tablets, which disintegrated in as little as five minutes and averaged a 25-minute disintegration time, and the Mylan Lots 367 and 368, none of which had disintegrated during the 30-minute administration period. DTX 680 at MYLAN 518160.

[20]Because of the unique buccal dosage form, standard *in vitro* dissolution tests (involving placing tablets in a large volume of buffer solution) were not suitable for measuring the rate of tablet disintegration. D.I. 148 at 463:1-464:5 and 478:10-17. Therefore, Mylan developed a special *in vitro* "screen test," in which the tablets were placed on a screen in a petri dish containing only enough water to contact approximately 20% of the tablet height. D.I. 148 at 478:10-480:9. Plaintiffs criticize this test by eliciting an unexplained conclusory opinion from Dr. Illum (D.I. 149 at 577:4-12), but do not offer any reason that the dramatic differences in disintegration times for the Fentora® tablets and the Lots 367 and 368 tablets measured by this test do not simulate their performance *in vivo*. Plaintiffs do not direct criticism to their own "specially developed" disintegration test, the results of which Plaintiffs wish to rely on in the Ireland study. PTX 266A at 3. Plaintiffs, however, unlike Mylan, have provided no information regarding the details of how that study was designed, conducted or interpreted.

time for tablet administration, *i.e.*, 15-30 minutes. Mylan's studies show that the effervescence in its tablets is required to achieve this rapid disintegration. If sodium starch glycolate is a "super-disintegrant," then effervescence could be characterized as a "super-duper-disintegrant." Accordingly, Mylan moved to an effervescent formulation to increase the speed of tablet disintegration.[21] D.I. 148 at 482:2-10. Effervescence was the best way for Mylan to achieve rapid tablet disintegration, and Mylan was entitled to use effervescence for this well-known prior art function in its product. *Id*.

After making the decision to pursue an effervescent formulation, Mylan scaled up and tested three effervescent formulations. D.I. 148 at 482:2-486:6; DTX 680 at MYLAN 518090. The first two effervescent lots Mylan tested, Lots 489 and 490, delivered a greater amount of fentanyl than necessary to meet the bioequivalence standard for Fentora®. D.I. 148 at 485:14-19; PTX 55. For Lot 544, Mylan used the same ingredients in the same amounts as in Lot 489, but increased the particle size of the fentanyl drug substance. D.I. 148 at 485:20-486:3. Once the particle size was adjusted, Lot 544 was bioequivalent to Fentora®. D.I. 148 at 486:4-6.

In their opening brief, Plaintiffs quote statements that they have taken out of context from Mylan's development documents, in particular, from a PowerPoint presentation prepared by Dr. Danny Kuntz during his work on a generic version of Abstral®. D.I. 153 at 27. The critical fact that Plaintiffs overlook in mischaracterizing these statements as "admissions," is that throughout the

[21] Both formulators working on the project, Ms. Bartley and her supervisor Dr. Twist, testified that Mylan could have developed a non-effervescent formulation that is bioequivalent if they had continued on that development path. D.I. 148 at 386:6-9, 515:2-516:4. There can be no doubt that effervescence is not required for the transmucosal delivery of fentanyl because there are several FDA approved fentanyl transmucosal products on the market that are not effervescent. D.I. 147 at 102:3-21. In addition to Actiq® and Fentora®, the FDA has also approved Abstral® (a fentanyl sublingual tablet), Onsolis® (fentanyl buccal film), Lazanda® (fentanyl nasal spray), and Subsys® (fentanyl sublingual spray). *Id*. Effervescence is also not required to make a product that is bioequivalent to Fentora® as Watson was granted FDA approval for a non-effervescent fentanyl buccal tablet that is bioequivalent to Fentora®. *Cephalon, Inc. v. Watson Pharms., Inc.*, 769 F. Supp. 2d at 747-751.

entire development process, each and every time Mylan referred to an "effervescent" formulation or an "effervescent couple," the formulation contained not only citric acid and sodium bicarbonate (effervescent components), but also sodium carbonate (a pH modifier).[22] D.I. 148 at 431:3-8; 448:14-449:7. The combination of these three ingredients, in the amounts present in the Mylan formulations tested served two functions that are well known in the prior art: (1) effervescence from the sodium bicarbonate and citric acid caused faster tablet disintegration; and (2) sodium carbonate, a pH modifier, raised the pH of saliva to the optimum range for fentanyl absorption. D.I. 148 at 448:14-449:7. It is therefore, incorrect for Plaintiffs to attribute Mylan's statements to the effects of "effervescence" alone.

IV. ARGUMENT

A. Legal Standards

1. Burden of Proof

Cephalon has the burden of proving infringement by a preponderance of the evidence. *See S. Bravo Sys. v. Containment Techs. Corp.*, 96 F.3d 1372, 1376 (Fed. Cir. 1996). "To prove infringement, the patentee must show that an accused product embodies all limitations of the claim either literally or by the doctrine of equivalents." *Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1340 (Fed. Cir. 2013), *citing TIP Sys. v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1379 (Fed. Cir. 2008). Therefore, "if any claim limitation is absent from the accused device, there

[22] Plaintiffs also erroneously argue that Mylan originally sought a label that incorporated the dynamic pH theory and then removed that language after the litigation began. D.I. 153 at 21. Mylan, however, is required by statute to include in its ANDA "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug" with very limited exceptions. *See* 21 U.S.C.§ 355(j)(2)(A)(v) (2011). The language Plaintiffs cite is taken verbatim from Plaintiffs' label, and although Mylan later amended the language in its own label to better describe the Mylan ANDA product, Plaintiffs presented no evidence at trial that the initial inclusion of that language was anything other than Mylan's copying the Fentora® label. Plaintiffs had the opportunity to determine why the language was initially included and then deleted (*e.g.*, at the deposition of Mr. Wayne Talton, Mylan's Vice President of Regulatory Affairs). Instead, Plaintiffs offer only their speculation.

is no literal infringement as a matter of law." *Id.*; *see also Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000).

2. Direct Infringement

An infringement determination requires a two-step analysis. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995); *see also Terlep v. Brinkmann Corp.*, 418 F.3d 1379, 1381 (Fed. Cir. 2005). "First, the claim must be properly construed to determine its scope and meaning." *Carroll Touch, Inc. v. Electro Mech. Sys.*, 15 F.3d 1573, 1576 (Fed. Cir. 1993); *see also Markman*, 52 F.3d at 976. Second, the claim, as properly construed, must be compared to Mylan's ANDA product. *See Markman*, 52 F.3d at 976; *Carroll Touch, Inc.*, 15 F.3d at 1576. Comparison of the claims to Mylan's ANDA product is a question of fact. *See Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998). "[A] dependent claim contains all of the limitations of the claim from which it depends." *Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). Accordingly, if Mylan's ANDA product does not infringe an independent claim, the product does not infringe any claim dependent thereon. *Id.* Moreover, "bioequivalencey is a regulatory and medical concern aimed at establishing that two compounds are effectively the same for pharmaceutical purposes." *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1298 (Fed. Cir. 2009). Therefore, "FDA equivalence is irrelevant to patent law because it involves fundamentally different inquiries." *Johns Hopkins Univ. v. Datascope Corp.*, 543 F.3d 1342, 1349 n.3 (Fed. Cir. 2008).

3. Inducement of Infringement

Cephalon also asserts that Mylan indirectly infringes the patents-in-suit by inducing infringement. 35 U.S.C. § 271(b) provides that "whoever actively induces infringement of a patent shall be liable as an infringer." "[T]here can be no indirect infringement without direct infringement." *Akamai Techs. v. Limelight Networks, Inc.*, 692 F.3d 1301, 1308 (Fed. Cir. 2012). To prevail on a theory of induced infringement, Cephalon has the burden of proving that Mylan's

actions will induce a third party to infringe the method claims and that Mylan knew or should have known that its actions would induce actual infringement. *See Warner-Lambert Co. v. Apotex Corp*, 316 F.3d 1348, 1363 (Fed. Cir. 2003). Cephalon must establish that Mylan possesses "specific intent to encourage another's infringement" and "not merely" that Mylan has "knowledge of the acts alleged to constitute inducement." *DSU Med. Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1305 (Fed. Cir. 2006) *citing Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed. Cir. 1990). Cephalon, thus, must prove that Mylan "knowingly aided and abetted another's direct infringement of the patent." *Rodime PLC v. Seagate Tech., Inc.*, 174 F.3d 1294, 1306 (Fed. Cir. 1999).

B. Cephalon Has Not Met Its Burden of Proving That Mylan's ANDA Product Contains an "Effervescent Agent In An Amount Sufficient to Increase Absorption" as Required by All Asserted Claims

1. Plaintiffs' Argument That Effervescence Increases Absorption In Mylan's Product (and Fentora®) Is Based On Unproven Theories

a. The Khankari Patents Identify Four Theories By Which Effervescence Hypothetically Could Increase Drug Absorption By Physically Altering the Oral Tissue

The idea of using effervescence to increase drug absorption originated, at least in part, from studies conducted by Dr. Jonathan Eichman, one of the named inventors on the Khankari patents, in support of his thesis, entitled "Mechanistic Studies on Effervescent-Induced Permeability Enhancement." *Cephalon, Inc. v. Watson Pharms., Inc.*, 769 F. Supp. 2d at 758-759. Professor Joseph Robinson, another named inventor, was Dr. Eichman's thesis advisor. Drs. Eichman and Robinson conducted tests to determine whether effervescence enhanced absorption of certain

compounds across the membrane of rabbit intestine and later published their results in an article with the same title as Dr. Eichman's thesis in 1998.[23] DTX 207.

The "Summary of the Invention" of the Khankari Patents provides that "[t]he pharmaceutical compositions of the present invention comprise an orally administrable medicament in combination with an effervescent agent used as penetration enhancer to influence the permeability of the medicament across the buccal, sublingual, and gingival mucosa."[24] JTX 2 at col. 2, ll. 7-11. The patents then identify four hypothetical mechanisms by which the evolution of carbon dioxide gas is purported to enhance oral drug absorption. D.I. 149 at 729:7-730:8; JTX 2 at col. 2, ll. 16-27. The "Detailed Description of the Invention" explains that:

> One aspect of this invention is to use effervescent as penetration enhancers for influencing oral drug absorption. Effervescent agents can be used alone or in combination with other penetration enhancers, which leads to an increase in the rate and extent of absorption of an active drug. It is believed that such increase can rise from one or all of the following mechanisms:
>
> 1. reducing the mucosal layer thickness and/or viscosity;
> 2. tight junction alteration;
> 3. inducing a change in the cell membrane structure; and
> 4. increasing the hydrophobic environment within the cellular membrane.
>
> The present dosage forms should include an amount of an effervescent agent effective to aid in penetration of the drug across the oral mucosa.

JTX 2 at col. 2, ll. 16-31.

b. Plaintiffs Abandoned the Four Theories Described in the Patents

At trial, Plaintiffs made little mention of the four theoretical mechanisms identified in the Khankari Patents. Furthermore, when Mylan's expert, Dr. Johnston, explained why none of the

[23] Eichman and Robinson did not conduct any experiments with fentanyl. DTX 207 at CEP-FEN00966595 (fentanyl is not listed as a substance used in the experiments).

[24] A penetration enhancer is generally referred to as a chemical entity that somehow changes the structure and function of the mucosal layer to help a drug pass through that layer. D.I. 149 at 728:21-729:4.

four theories are correct, Plaintiffs' experts did not attempt to defend those theories, and Plaintiffs' counsel appeared to criticize Dr. Johnston on cross examination for even bringing up the issues. D.I. 149 at 757:7-761:9.

The first hypothetical mechanism is that the bubbling of carbon dioxide "reduc[es] the mucosal layer thickness and/or viscosity." D.I. 149 at 731:2-18; JTX 2 at col. 2, ll. 16-27. Plaintiffs have presented no evidence that they ever even attempted to measure the thickness or viscosity of the mucosal layer. D.I. 149 at 731:2-18. Plaintiffs also presented no evidence that bubbling of carbon dioxide would alter that layer. *Id*. In fact, Eichman and Robinson's 1998 publication concludes that the bubbling of carbon dioxide gas neither thins nor strips the mucosal layer, nor does it contribute to an increase in drug flux. D.I. 149 at 731:2-733:7; DTX 207 at CEP-FEN00966595 ("Mechanistic studies indicated that effects due to CO_2 bubble evolution such as…mucus thinning/stripping…did not contribute to increases in drug flux.").

The second hypothetical mechanism is that the bubbling of carbon dioxide alters tight junctions. D.I. 149 at 733:8-734:6; JTX 2 at col. 2, ll. 16-27. Tight junctions are "gatekeepers" between the cells of the epithelial layer and only impact the paracellular pathway. D.I. 149 at 733:9-734:11. As Dr. Johnston explained without contradiction, human oral mucosa is devoid of tight junctions, making it impossible that effervescence could increase drug absorption in that manner, particularly when fentanyl is delivered via the transcellular pathway, not the paracellular pathway. *Id*.

The third hypothetical mechanism identified in the Khankari Patents is that carbon dioxide "induc[es] a change in the cell membrane structure." D.I. 149 at 734:14-735:15; JTX 2 at col. 2, ll. 16-27. The Khankari Patents include no experimental data showing the carbon dioxide generated from an effervescent reaction alters the cell membrane structure in any way. D.I. 149 at 734:14-735:1. Furthermore, Drs. Eichman and Robinson concluded that there was no change in the cell

membrane structure based on the experimental evidence they obtained. D.I. 149 at 735:2-15; DTX 207 at CEP-FEN00966595 ("Cellular enzyme (5'-ND and LDH) and total protein release assays did not indicate cell membrane perturbation and/or damage.").

The fourth hypothetical mechanism identified in the Khankari Patents is that carbon dioxide "increas[es] the hydrophobic environment within the cellular membrane." D.I. 149 at 735:17-736:4; JTX 2 at col. 2, ll. 16-27. Again, the Khankari patents provide no data and Plaintiffs provided no other evidence that carbon dioxide can increase the hydrophobic environment within the cell membrane. D.I. 149 at 735:17-736:4. Additionally, there is no evidence in the scientific literature to support the hypothesis that carbon dioxide can have such an effect.[25] *Id*. Even if carbon dioxide penetrated into the cellular membrane, there is no reason to expect that it would alter the hydrophobicity, because the interior of the cell membrane is already very hydrophobic and carbon dioxide is a small, uncharged molecule that would not be expected to increase that hydrophobicity. D.I. 149 at 738:21-740:11. Finally, the Absorption Systems study conducted by Plaintiffs conclusively demonstrates that effervescence does not increase drug absorption across the buccal membrane through alteration of the hydrophobic environment.[26] D.I. 149 at 736:5-738:13.

[25] At trial, Dr. Illum vaguely suggested that effervescence could increase absorption through the buccal mucosa because the bubbles produced by carbon dioxide gas leaving solution may disturb a so-called stagnant surface layer on the buccal mucosa. D.I. 149 at 582:6-583:10. Dr. Illum failed to identify any evidence or cite any literature in support of her speculative theory. *Id*. Nonetheless, Dr. Johnston interpreted Dr. Illum's comments as a reference to a paper by Schürmann and Turner (D.I. 149 at 741:2-21; PTX 345), and he explained why Dr. Illum was wrong. *Id*. at 742:8-744:25. As Dr. Johnston testified, the Schürmann and Turner paper does not even mention effervescence, much less describe how it could be used to increase drug absorption across cell membranes. *Id*. at 744:20-25; PTX 345. Moreover, authors of the paper describe the existence of such a stagnant layer as a "hypothetical" possibility. *Id*. at 742:8-743:9; PTX 345 at CEP-FEN01389467-468. There is no agreement among scientists that such a stagnant layer even exists. D.I. 149 at 743:10-744:19.

[26] *See* Section IV(B)(3)(b)(i), *infra*.

c. At Trial, Plaintiffs Relied on Their "Dynamic pH" Theory

Perhaps already realizing that the four theoretical mechanisms identified in the Khankari Patents were not valid, Plaintiffs came up with yet another theory as a possible explanation for why effervescence has a greater effect on absorption than its already well-known effect on tablet disintegration. Plaintiffs refer to that theory as the "dynamic pH effect."

According to Plaintiffs' theory, the effervescent reaction initially lowers the pH in the area surrounding the tablet (an initial "drop" in the pH during the first minute or less) as a result of the formation of carbonic acid in saliva. D.I. 147 at 164:8-17, 193:1-194:6. Plaintiffs' theory is then that as the carbonic acid breaks down and carbon dioxide leaves the solution, the pH begins to rise. D.I. 147 at 163:20-164:1, 164:18-20. Plaintiffs allege that the initial lowering of pH facilitates dissolution of fentanyl citrate, and the subsequent increase in pH converts ionized fentanyl to unionized fentanyl that can be absorbed through the oral mucosa. D.I. 147 at 163:9-164:7.

Plaintiffs' "dynamic pH" theory suffers from three major defects, which Plaintiffs made no attempt to address at trial. *First*, there is no evidence that the pH profiles seen in *in vitro* tests even occur in the mouth when a tablet is administered. As Dr. Weiner explained in undisputed testimony, there is no basis for believing that they would occur. D.I. 150 at 795:4-796:14. *Second*, there is no evidence that the pH profiles seen *in vitro* are attributable to effervescence. As Dr. Weiner explained, again in undisputed testimony, those pH profiles are simply the result of differences in the solubilities and therefore the rates of dissolution of acids and bases in the tablets. D.I. 150 at 810:16-813:20. *Third*, there is no evidence that a dynamic pH shift, even if it occurred in the mouth, would enhance the absorption of fentanyl. D.I. 150 at 836:2-840:12.

d. Plaintiffs Failed to Prove that Effervescence Causes a Dynamic pH Effect, and Presented No Evidence that A Dynamic pH Effect, Even if it Did Occur, Would Increase Drug Absorption

(i) Plaintiffs Never Tested the "Dynamic pH" Theory In the Mouth

Plaintiffs have touted their "dynamic pH" theory in literature published by Cephalon and Cima for many years, but they have never done tests necessary to prove that it actually occurs -- it remains an unproven hypothesis. In fact, in the section of its Fentora® NDA describing the function of the tablet excipients, Cephalon explained:

> The enhanced absorption seen in the clinical studies with the proposed dosage form is hypothesized to be due to a combination of effervescence and a dynamic change of pH. Upon placement of the tablet on the buccal surface, the effervescent reaction is initiated, causing liberation of carbon dioxide. This release facilitates disintegration of the tablet, and is hypothesized also to provide a decrease in pH in the microenvironment around the tablet, thus driving the fentanyl into solution. As the effervescent reaction continues and the other pH modifying substances dissolve, a subsequent rise in pH increases the fraction of the fentanyl dose that is non-ionized and thus facilitates its rapid absorption through the buccal mucosa.

PTX 259 at CEP-FEN00029795 (emphasis added). In their NDA, Plaintiffs correctly told the FDA, that the effervescence functions as a disintegrant and any increase in drug absorption due to a dynamic pH theory is nothing more than a "hypothesis." D.I. 149 at 644:1-645:9; PTX 259 at CEP-FEN00029795. At trial, however, Plaintiffs presented no evidence that this "dynamic pH" shift, even if it did occur *in vitro*, would occur *in vivo*, in the mouth. Dr. Khankari admitted that Plaintiffs never determined the pH of Fentora® in the mouth, because he said that placing a pH probe in the mouth with a Fentora® tablet to determine what happens to the pH would be too difficult. D.I. 147 at 192:17-20. Thus, it its undisputed that Plaintiffs never measured the pH or any pH changes in the mouth of any patient receiving Mylan's ANDA product, or the Fentora® tablet. As discussed below, because of the elevated temperature in the mouth (at which the already poorly soluble

carbon dioxide would be even less soluble) and the buffering capacity of saliva, there is no basis for assuming that effervescence would cause any pH shifts in the saliva in the mouth. D.I. 150 at 804:12-806:6.

(ii) Plaintiffs Presented No Evidence at Trial That Effervescence (the bubbling of CO_2) Changes pH

Moreover, Plaintiffs have failed to show that the so-called dynamic pH changes that are seen in simple *in vitro* tests are caused by effervescence. As Mylan's expert, Dr. Weiner, explained, Plaintiffs' "dynamic pH" theory has no scientific basis, because effervescence is not capable of causing the pH changes that Plaintiffs attribute to the effervescent couple. D.I. 150 at 795:13-16, 806:24-807:3, 820:2-12. Rather, any pH changes are simply the result of differences in the solubilities of the acids and bases in the tablets. D.I. 150 at 812:5-813:8.

Plaintiffs' "dynamic pH" shift consists of two phases, an initial drop in pH, followed by a rise.[27] For effervescence to cause an initial drop in pH (just the first phase of Plaintiffs' hypothetical "dynamic pH" theory) three reactions must occur. First, CO_2 must dissolve in water.[28] D.I. 150 at 799:15-800:1. However, as Dr. Khankari agrees, the CO_2 bubbles that are created by the effervescent reaction, however, are in the gaseous state and are not dissolved in water. D.I. 147 at 194:11-19. As Dr. Weiner explained, the solubility of carbon dioxide in an aqueous medium (e.g., water or human saliva) is very low, which means that very little of the carbon dioxide that is formed from the effervescent reaction will actually go into solution.[29] D.I. 150 at 798:17-799:14.

[27] Although Plaintiffs refer to the second phase as a "gradual" rise that is not what is seen in Plaintiffs' *in vitro* tests. The initial drop and sharp rise in pH occurs during the first minute. PTX 263 at CEP-FEN00374120-121.

[28] Dr. Khankari and Dr. Illum agree that for carbon dioxide to react with the water to form carbonic acid, the carbon dioxide must be dissolved in the water. D.I. 147 at 194:3-10; D.I. 149 at 559:23-560:13.

[29] In a pressurized system (*e.g.*, a bottle of seltzer water), a greater than normal amount of carbon dioxide is dissolved in solution because the pressure forces the carbon dioxide into solution. D.I. 150 at 798:16-799:12. The human mouth is under atmospheric pressure which is not sufficient to

Furthermore, solubility decreases as temperature increases, so the solubility of carbon dioxide in the mouth[30] would be even less than that seen in *in vitro* experiments (conducted at room temperature). D.I. 150 at 806:4-11. Next, any carbon dioxide that has dissolved in saliva must then react with water to form carbonic acid. D.I. 150 at 799:15-800:16. However, the reaction that converts dissolved carbon dioxide and water to carbonic acid is a very slow reaction that proceeds to a very small extent. *Id.* To produce one molecule of carbon dioxide, approximately 600 molecules of carbon dioxide have to be dissolved in saliva, and this would have to happen within the first minute or less of tablet administration when the pH initial drop occurs. *Id.* Because the formation of carbonic acid is not favored, the decomposition of carbonic acid (back into carbon dioxide and water) is very favorable and occurs within seconds.[31] D.I. 150 at 801:3-19. Last, any carbonic acid that formed must then dissociate to form hydrogen ions. D.I. 150 at 801:20-802:2. Carbonic acid, however, is weak acid, and a weak acid will only dissociate to a small extent in an aqueous solution. D.I. 150 at 801:20-803:21. That means that very little hydrogen ion is released from carbonic acid to lower the pH.[32] D.I. 150 at 802:3-21. Accordingly, all three of the reactions that would be required for effervescence to create a drop in pH, actually favor the opposite reaction.

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force a significant amount of carbon dioxide into saliva. *Id.* Plaintiffs' expert, Dr. Olsen, also agrees that the solubility of carbon dioxide in water is low. D.I. 148 at 381:5-8.

[30]Human saliva is at body temperature, or close to it. D.I. 150 at 805:2-4. Unlike a solid substance (*e.g.*, sugar crystals), when a gas such as carbon dioxide is heated, the solubility will actually decrease. D.I. 150 at 805:8-806:6. Accordingly, at body temperature the already low solubility of carbon dioxide in saliva will be further decreased. Plaintiffs have produced no evidence demonstrating the effect on saliva pH when carbon dioxide is bubbled through saliva. D.I. 150 at 806:7-11.

[31]Dr. Khankari admitted that the reaction of carbon dioxide and water to form carbonic acid is a reversible reaction (D.I. 147 at 195:10-24) and that the reaction equilibrium favors the formation of carbon dioxide and water over that of carbonic acid. D.I. 147 at 196:24-198:21.

[32]The pH is a measure of the concentration of hydrogen ions in solution. D.I. 150 at 798:11-15. Citric acid is also a weak acid, but it is about one thousand times stronger than carbonic acid. D.I. 150 at 802:22-803:6. Accordingly, hydrogen ions dissociate from citric acid much more readily than that from carbonic acid.

Additionally, human saliva is naturally buffered to resist pH changes. D.I. 150 at 804:12-805:1. Therefore, addition of a weak acid like carbonic acid would not be expected to significantly change the pH of human saliva due to its buffering capacity. *Id.* Dr. Weiner's testimony regarding these points were not disputed, or even addressed, by Plaintiffs' witnesses.

Plaintiffs rely on certain *in vitro* microenvironment pH profiles to illustrate their "dynamic pH" theory.[33] D.I. 149 at 711:8-712:8; DTX 57 at CEP-FEN01146466. Effervescence, however, cannot be responsible for a drop of 3 full pH units as seen in Plaintiffs' microenvironment pH tests.[34] D.I. 150 at 808:14-20. A much more likely explanation for the observed pH drop is the rapid dissolution of the very soluble citric acid from the tablet into solution.[35] D.I. 150 at 808:21-811:16. Indeed, of the three components in Fentora® and Mylan's ANDA product that are capable of effervescence (citric acid, sodium carbonate, sodium bicarbonate) citric acid is by far the most soluble -- twice as soluble as the two basic substances. D.I. 150 at 808:21-811:16, 812:22-24. Accordingly, the initial pH drop has nothing to do with effervescence, but rather is solely attributable to citric acid dissolution. D.I. 150 at 808:21-811:16, 812:5-813:8.

Effervescence (the evolution of carbon dioxide) also cannot be responsible for the sharp rise in pH that occurs after the initial pH drop, both of which occur in less than one minute. D.I. 150 at 812:18-813:8. Rather, as Dr. Weiner explained, the subsequent increase in pH is attributable to the

[33] To obtain these pH profiles, various tablet formulations are dropped in 2 milliliters of buffer and the pH is recorded. D.I. 150 at 807:16-808:12; DTX 57 at CEP-FEN01146448.

[34] The pH profiles shows that for tablet labeled ET which contains citric acid, sodium bicarbonate, and sodium carbonate, the pH drops from 7 to about 4 in less than a minute. D.I. 149 at 673:7-674:7; DTX 57 at CEP-FEN01146466.

[35] The pH profile of the citric acid only tablet, labeled "CA," drops to around 2 which is the expected pH when citric acid goes into solution. D.I. 150 at 808:21-811:16; DTX 57 at CEP-FEN01146466. Thus, it is clear that citric acid dissolution is responsible for lowering the pH in the microenvironment tests.

later dissolution of the two bases -- sodium bicarbonate and sodium carbonate.[36] D.I. 150 at 813:9-20, 817:8-15. Sodium bicarbonate and sodium carbonate are both water soluble, but considerably less so than citric acid. But because they are bases, as they dissolve, the pH increases. D.I. 150 at 812:17-813:20, 817:8-15. Dr. Illum agrees. D.I. 149 at 625:14-626:19.

Studies conducted by Cephalon further support Dr. Weiner's conclusion that it is the dissolution of the acid and bases (at different times based on their different solubilities) that are responsible for any pH changes seen *in vitro*, not effervescence. DTX 535 at CEP-FEN00466053-54. Dr. Khankari and his colleagues conducted experiments called "Wetted Oravescent Tablet pH Plots," in which they placed strips of litmus paper on top of Fentora® tablets and then wetted the tablets with drops of water. *Id*. The investigators then took color digital photographs of the dissolving tablets at four different time points after wetting at ten seconds, one minute, three minutes and six minutes. *Id*.

The photographs of the litmus paper wetting tests illustrate Dr. Weiner's point that the changes in pH of the tablet are due to the differential solubilities as each of the various tablet excipients, *e.g.*, citric acid (shown in red) sodium bicarbonate (shown in blue), and sodium carbonate (also shown in blue). D.I. 150 at 817:16-819:5; DTX 313 at 3, Figure 1; DTX 535 at CEP-FEN00466055. The photographs show that citric acid dissolves first, creating regions of low pH (in red) followed by dissolution of the carbonates (in blue), creating regions of high pH on the tablet surface. *Id*. Indeed, in describing the results, Cephalon noted that regions of the tablet in close proximity to each other have different pH values, and that these differences are likely due to the contribution of individual components in the tablet to the pH. D.I. 149 at 631:2-11; DTX 535 at

[36] Evidence from Plaintiffs' microenvironment test, namely, the pH profile of the tablet labeled SC that contains only sodium carbonate, supports this conclusion. *Id.*; D.I. 149 at 673:7-15, 675:20-676:2; DTX 57 at CEP-FEN01146466. There is a rise in pH seen for SC tablet, but there is no citric acid present to produce effervescence. *Id*. Therefore, the rise in pH cannot be the result of effervescence, and must be due to the dissolution of sodium carbonate. *Id.*

CEP-FEN00466053. Cephalon also noted that the lower pH regions correspond to citric acid locations, and the higher pH regions correspond to sodium carbonate and bicarbonate localities. D.I. 149 at 631:12-18; D.I. 150 at 818:9-23; DTX 535 at CEP-FEN00466054.

The *in vitro* pH profile of the first non-effervescent formulation tested by Mylan, Lot 306, also support Dr. Weiner's conclusion that it is the dissolution of the acid followed by the dissolution of the bases, not effervescence, that is responsible for the initial pH drop and subsequent rise (the "dynamic pH") seen in Plaintiffs' and Mylan's *in vitro* tests. Lot 306 contained *inter alia,* fentanyl (fine grade), ascorbic acid and magnesium oxide (pH modifiers), sodium starch glycolate (disintegrant), and sorbitol (a filler). DTX 755 at MYLAN 479068. The pH profile for this non-effervescent formulation, however, had a rapid initial drop identical to that seen with the effervescent formulations. DTX 680 at MYLAN 518096. The initial drop was followed by a rise. *Id*. In other words, this non-effervescent formulation exhibited a "dynamic pH." *Id*. The "dynamic pH" profile seen in Lot 306 could not have been caused by effervescence (as Plaintiffs claim occurs with Fentora®). Instead, the initial drop is attributable to the dissolution of the very soluble ascorbic acid in the tablet (similar to citric acid) and the subsequent pH rise is due to the slower dissolution of the much less soluble magnesium oxide (a base). D.I. 150 at 846:11-25.

At trial, Plaintiffs did not dispute or offer any reason why differences in solubilities of citric acid and basic carbonate salts do not fully explain such pH changes seen in the *in vitro* tests of the Mylan product. In fact, Plaintiffs' expert Dr. Illum agreed at trial that citric acid dissolution will contribute to the low pH observed in the microenvironment pH profiles. D.I. 149 at 618:8-24. Dr. Illum also admitted that she does not know to what extent the pH drop is being caused by the effervescent reaction as compared to the dissolution of citric acid. D.I. 149 at 621:7-14, 623:11-625:5. Dr. Illum further admitted that sodium bicarbonate and sodium carbonate will dissolve into the solution and contribute to the pH of the solution. D.I. 149 at 625:14-23, 633:17-21.

Accordingly, in view of the evidence presented at trial, Plaintiffs have failed to prove that the rise and fall in pH observed in the Plaintiffs' microenvironment pH profiles results from effervescence. In fact the evidence shows that it is due to the dissolution of the highly soluble citric acid followed by the dissolution of sodium bicarbonate and sodium carbonate. D.I. 150 at 812:5-813:8, 817:8-15.

(iii) Plaintiffs Presented No Evidence That A "Dynamic pH" Shift Would Increase Fentanyl Absorption

Plaintiffs argue that an initial pH drop helps to dissolve the fentanyl citrate and that it is necessary to increase the pH slowly to prevent fentanyl from precipitating out of solution. D.I. 147 at 163:9-164:7; D.I. 149 at 558:23-559:13. Plaintiffs' argument that the pH shifts that are part of their "dynamic pH theory" enhance fentanyl absorption do not make scientific sense. The evidence shows that if an initial pH drop and subsequent rise occur at all, they are very short lived -- occurring within the first minute of tablet administration.[37] D.I. 150 at 836:2-25; DTX 57 at CEP-FEN01146466. As a result, such a drop, if it occurs, could only affect a small amount of fentanyl citrate on the tablet surface, whereas the vast majority of fentanyl citrate in the tablet, which dissolves over 15-30 minutes, would be unaffected. D.I. 150 at 838:23-839:4. Also contrary to Plaintiffs' position, the speed at which a pH is reached will have no impact on the precipitation of fentanyl. D.I. 150 at 839:8-16. The only factor that will determine absorption is the pH at the time of absorption. *Id.* As Dr. Weiner explained, the fentanyl molecule does not have a memory, so the pH of the saliva in the first minute will have no impact on the solubility or absorption of fentanyl at a subsequent point in time. D.I. 150 at 836:2-25. Even Dr. Illum admits that for fentanyl absorption, it does not matter that the pH initially dropped, so long as the unionized fentanyl is in solution. D.I. 149 at 653:16-19. Dr. Illum admits that during the brief time that the pH is low, there

[37] Due to the way the data is reported it is not possible to determine precisely when the low pH is observed. It is known only that the low pH is observed at some point within the first minute. However, it should be noted that at 1 minute the pH has risen sharply from the low point to a near final pH. DTX 57 at CEP-FEN01146466.

will be little fentanyl absorption, because the vast majority of the drug is in the non-absorbable ionized form. D.I. 149 at 619:3-13. In summary, even if Plaintiffs' "dynamic pH" shifts actually occurred *in vivo*, Plaintiffs have presented no evidence that they would have any effect on fentanyl absorption across the oral mucosa. D.I. 150 at 840:9-12.

Finally, it is not necessary to lower the pH initially to deliver fentanyl contained in Fentora® or Mylan's ANDA product. In both Fentora® and in Mylan's ANDA product, fentanyl is present in the tablet in the form of its soluble citrate salt. D.I. 150 at 837:1-4; PTX 264 at CEP-FEN00460695-697; PTX 293 at MYLAN 517118-121. Plaintiffs' NDA confirms that fentanyl citrate is water soluble, up to approximately 25,000 micrograms per milliliter. D.I. 150 at 837:5-10; D.I. 149 at 653:23-654:10; PTX 259 at CEP-FEN00029784. There is no dispute among the parties or the experts that the highest dosage strength available contains 800 micrograms of fentanyl citrate. D.I. 149 at 654:11-14; DTX 293 at MYLAN 517121.

Dr. Johnston, the only witness at trial who is an expert in the anatomy and physiology of the oral tissue, explained that the volume of saliva present in the mouth is generally considered to be about one milliliter.[38] D.I. 149 at 745:9-16. Plaintiffs' expert Dr. Illum suggested that the volume of saliva in the buccal cavity is small approximately 100 microliters.[39] D.I. 149 at 700:1-701:1. Dr.

[38] As Dr. Johnston explained, there is a major salivary gland, the parotid gland, that empties into the buccal cavity. D.I. 149 at 726:1-727:3. The placement of an effervescent tablet in the buccal area will stimulate saliva production due to mechanical pressure. D.I. 149 at 750:21-751:20. Effervescence is also known to stimulate saliva production, as acknowledged in the Khankari patents. D.I. 149 at 751:22-752:9; JTX 2 at col.1, ll. 38-43. Because the tablets will stimulate saliva production during this entire time, the volume of saliva produced in total would be sufficient to dissolve all of the fentanyl citrate in even the higher dosage tablet. D.I. 149 at 752:10-754:12.

[39] Dr. Illum had no support for her estimate or any experience on which to base that opinion. Additionally, Dr. Illum's 100 microliter estimate ignores that fact that: (1) saliva production is continuous; (2) saliva flows throughout the oral cavity; and (3) the Fentora® and Mylan tablets are administered for a period of 15 to 30 minutes. Therefore, it would be inappropriate to consider only the amount of saliva that comes into contact with the tablet at one single instant in time.

Johnston disagreed, and explained why Dr. Illum's estimate of the volume of saliva in the buccal cavity is incorrect. D.I. 149 at 745:14-754:12.

While recognizing that one cannot measure the exact volume of saliva in the buccal cavity at any one instant in time, Dr. Johnston explained that saliva is continually being produced at rate of anywhere from 100-1000 microliters per minute. D.I. 149 at 746:2-747:17. Additionally, saliva flow is also not a static system, rather saliva flows to all parts of the mouth and carries dissolved fentanyl with it, thus increasing the surface area available for fentanyl absorption. D.I. 149 at 746:2-750:14. Furthermore, both Fentora® and Mylan's ANDA product are administered for approximately 15 to 30 minutes and saliva will be produced and swallowed during the entire administration period. D.I. 149 at 746:2-22, 752:10-754:12. As Dr. Johnston explained, taking into account the amount of saliva produced during the entire administration period of 15 to 30 minutes, it is impossible that the volume of saliva in the buccal cavity that comes into contact with the Fentora® tablet over the whole administration period is only 100 microliters – indeed, the volume would be much greater. D.I. 149 at 745:14-754:12. Dr. Illum, admitted that at a pH of 7 and below, the amount of fentanyl in an 800 microgram tablet (or smaller) would dissolve in one milliliter of water or saliva. D.I. 149 at 655:16-25. Dr. Illum also agrees that the pH of saliva in healthy humans is usually in the range of about 6.7 to 7. D.I. 149 at 654:17-20. Accordingly, the fentanyl citrate in the Mylan ANDA product is soluble at the normal saliva pH in the volume of saliva that typically would be expected to come into contact with the tablet over the administration period.

(iv) Summary Regarding the "Dynamic pH" Theory

The claims require that the effervescent agents be employed in amounts sufficient to increase fentanyl absorption. Critical to Plaintiffs' argument is that effervescence causes a "dynamic pH" shift, which, in turn, enhances fentanyl absorption. However, Plaintiffs have failed to prove that: (1) the pH shifts seen *in vitro* even occur in the saliva in the mouth; (2) the pH shifts

are caused by effervescence as opposed to different rates of dissolution of the acids and bases; or (3) such pH shifts, even if they did occur, would cause an increase in fentanyl absorption. Thus, the central underpinning of Plaintiffs' infringement argument has failed.

2. The Overwhelming Scientific Evidence Demonstrates That The Only Beneficial Effect of Effervescence in Mylan's Product (and Fentora®) Is Its Prior Art Use to Speed Tablet Disintegration

a. Prior to Trial, Cephalon Agreed That Effervescence Is A Disintegrant

Plaintiffs told the FDA that the rationale for including the effervescent agents (*e.g.*, citric acid and sodium carbonate) in the Fentora® tablet is to "facilitate oral disintegration of the tablets." D.I. 149 at 643:14-647:22; PTX 259 at CEP-FEN00029795-796. Accordingly, Plaintiffs' Fentora® tablet merely takes advantage of the admittedly well-known prior art use of effervescence to speed tablet disintegration. Mylan's ANDA product does the same. D.I. 150 at 840:13-18.

The Khankari Patents state that "effervescents have been employed to obtain rapid dissolution and/or dispersion of [a] medicament in the oral cavity." JTX 2 at col. 1, ll. 38-40. For example, U.S. Patent 5,223,264 ("the '264 patent") is cited in the Khankari patents, and teaches a person of ordinary skill in the art that effervescence can be used to disintegrate a tablet rapidly in the human mouth.[40] D.I. 150 at 794:3-20; JTX 2 at col. 1, ll. 38-40; DTX 413 at col. 2, ll. 52-58. Thus, it is clear that the use of effervescence to speed tablet disintegration in the mouth was well known prior to the priority date of the Khankari patents. D.I. 150 at 793:12-19; DTX 413. Dr. Khankari admitted this at trial. D.I. 147 at 191:13-17. In fact, Dr. Khankari admitted that Cima had previously used effervescence for that very purpose. D.I. 147 at 150:17-151:8, 191:2-9.

[40] *See* Footnote 9, *supra*.

b. Mylan's Product Development Data Demonstrates That Effervescent Tablets Disintegrate Faster Than Tablets Without Effervescence

As part of Mylan's pharmacokinetic study to evaluate the non-effervescent Lots 367 and 368, Mylan recorded *in vivo* disintegration times for all of the tablets. DTX 680 at MYLAN 518160. Not a single tablet of the non-effervescent Mylan Lots 367 and 368 completely disintegrated within the allotted 30 minutes. D.I. 148 at 474:3-477:7; DTX 680 at MYLAN 518160. In contrast, the effervescent Fentora® tablets disintegrated much more rapidly with an average disintegration time of 25.5 minutes, and some Fentora® tablets disintegrated in as little as 5 minutes. D.I. 148 at 477:8-478:7; DTX 680 at MYLAN 518160

Plaintiffs argue that the differences between the disintegration times for Mylan Lots 367 and 368 were not significantly different than the disintegration time for Fentora® because a number some of the Fentora® tablets that were tested also did not completely disintegrate within 30 minutes. D.I. 153 at 25-26. Plaintiffs' argument overlooks that the actual differences in the disintegration times could be much greater than what is reflected by the averages presented. The study protocol only allowed 30 minutes for tablet disintegration before subjects were instructed to swallow the remaining tablet. D.I. 148 at 468:14-470:18; DTX 547 at MYLAN 095423-24; DTX 549 at MYLAN 499059. When that occurred, the tablet disintegration time was recorded as 30 minutes. *Id.* Because any remaining tablet was swallowed after 30 minutes, it is not possible to determine what the true difference in the disintegration times would have been if the tablets had not been swallowed. D.I. 148 at 474:3-477:7. Moreover, even though some of the Fentora® tablets had not completely disintegrated in 30 minutes, some of them had, and, on average, they disintegrated in about 25 minutes. D.I. 148 at 477:8-478:7; D.I. 150 at 850:17-851:12; DTX 680 at MYLAN 518160. Accordingly, the overall rate of disintegration for the Fentora® tablet was considerably faster than the rate of disintegration of Mylan Lots 367 and 368. D.I. 150 at 850:17-852:12. Even

Dr. Illum admitted that the rate of disintegration for a tablet that takes 30 minutes to completely disintegrate will be faster than one that takes longer than 30 minutes to disintegrate. D.I. 149 at 685:1-10.

As discussed in Section III(D) above**,** Mylan developed a special "screen test" to better evaluate the disintegration characteristics of the Mylan non-effervescent formulations. D.I. 148 at 478:10-481:6. The *in vitro* disintegration test results vividly demonstrate that the effervescent Fentora® tablet disintegrated much more rapidly than the non-effervescent Lots 367 and 368.[41] *Id.*; DTX 32 at MYLAN 026040. The rapid disintegration of the Fentora® tablet was attributed to its effervescence. Mylan therefore decided to incorporate effervescence into its formulation to improve tablet disintegration. D.I. 148 at 481:21-482:10. The screen test results confirm that the lower pharmacokinetic values seen for Mylan lots 367 and 368 were due to poor tablet disintegration. D.I. 148 at 481:13-20; D.I. 150 at 849:4-15.

c. The Mere Presence Of A Superdisintegrant Does Not Mean That Effervescence Is Not Required For Tablet Disintegration

Plaintiffs argue that the superdisintegrant included in the Mylan ANDA product was sufficient to disintegrate the tablet, and thus effervescence is not required for disintegration. D.I. 153 at 25-27, 44-47. Plaintiffs' argument is belied by the data presented at trial. As discussed above, two of Mylan's non-effervescent formulations that contained 5% sodium starch glycolate, Lots 367 and 368, failed to achieve adequate disintegration within the requisite administration time in both *in vitro* and *in vivo* tests.[42] D.I. 148 at 481:7-12, DTX 680 at MYLAN 518089. Thus, Plaintiffs' argument that the mere presence of 5% sodium starch glycolate is sufficient to

[41] Plaintiffs state that Mylan has never documented in writing that Mylan Lots 367 and 368 had a disintegration problem. D.I. 153 at 26, n.4. It is said that a picture is worth a thousand words. The Mylan screen test photographs clearly and unambiguously depict the disintegration problem with Mylan Lots 367 and 368 (DTX 32 at MYLAN 026040) and amply recorded that problem.
[42] In contrast, the Mylan ANDA product contains 4%. DTX 680 at MYLAN 518090 (Lot 544).

disintegrate the Mylan ANDA product within the time period that the tablet is administered is wrong. D.I. 150 at 855:1-9.

Plaintiffs seek to attribute the disintegration problems in Lots 367 and 368 to other tablet components and assert that 5% sodium starch glycolate must be sufficient to disintegrate Mylan's ANDA tablets because a different non-effervescent formulation containing 5% sodium starch glycolate, Lot 306, did not have problems with disintegration. D.I. 153 at 45-46. Plaintiffs' argument, in addition to contradicting the clear *in vitro* and *in vivo* disintegration data presented for Lots 367 and 368, is completely unsupported. *Id.* Plaintiffs' speculative argument assumes that a component of the Lot 367 and 368 formulations slows disintegration. However, a more likely explanation is that components of Lot 306 speed disintegration.

Plaintiffs also argue that Mylan has not presented any evidence that the 4% sodium starch glycolate in Mylan's ANDA product do not adequately disintegrate the tablets. D.I. 153 at 45. This is improper burden shifting. The burden is on Plaintiffs to show that the sodium starch glycolate in Mylan's ANDA product disintegrates the tablets within the required time frame (i.e., 15 to 30 minutes) without the aid of effervescence. Nonetheless, Mylan has presented evidence that two non-effervescent formulations that contain more sodium starch glycolate than the Mylan ANDA product do not effectively disintegrate. D.I. 148 at 481:7-12. Mylan has also presented evidence that effervescence is effective at speeding the disintegration of tablets. DTX 32 at MYLAN 026040. Accordingly, despite not having the evidentiary burden, Mylan has shown that effervescence is required for disintegration of the Mylan ANDA product within the time frame allowed for tablet administration.

Finally, Plaintiffs seem to argue that a tablet with 4% of a superdisintegrant will eventually disintegrate, so effervescence is not needed for disintegration. D.I. 153 at 45-47. That argument, however, ignores the whole point of the claim requirement that drug absorption must be

"increased." The goal and alleged advantage of a tablet for treating breakthrough cancer pain is to get the drug into systemic circulation rapidly. Achieving this goal requires not only disintegration of the tablet, but rapid disintegration. Mylan has shown that the effervescence in its tablets is required to achieve disintegration within the time that the drug is intended to be delivered, *i.e.*, 15 to 30 minutes. PTX 249 at MYLAN 516939.

3. Plaintiffs Misinterpret and Mischaracterize Experimental and Clinical Results Presented at Trial

a. Fentanyl Absorption Requires Both Rapid Disintegration and A pH That Favors The Absorption Of Fentanyl

As Dr. Weiner explained, a tablet must possess two characteristics to deliver fentanyl effectively across the oral mucosa: (1) the tablet must rapidly disintegrate, and (2) the tablet must contain excipients that will adjust and maintain saliva pH to an optimal pH range for fentanyl absorption. D.I. 150 at 820:23-822:19. Both of these concepts were well known in the prior art. D.I. 150 at 825:19-22.

Rapid tablet disintegration is necessary to get fentanyl into solution as quickly as possible. D.I. 150 at 820:23-821:25. It is necessary to get fentanyl into solution quickly because fentanyl cannot exert an effect unless it is first in solution. *Id.* Accordingly, the faster a tablet disintegrates, the faster fentanyl can go into solution and exert an effect. Dr. Illum agrees that an important factor in the delivery of fentanyl across the oral mucosa is the disintegration of the tablet. D.I. 149 at 642:10-18.

Effective fentanyl absorption also requires adjustment of the pH of the saliva to an optimum range as quickly as possible, and maintaining the pH within that range as long as possible. D.I. 150 at 820:23-822:19, 839:17 - 840:8. The optimum pH is the pH at which the maximum amount of unionized fentanyl (*i.e.*, fentanyl free base) is dissolved in solution, without any unionized fentanyl

precipitating out of solution. D.I. 150 at 831:1-6. Importantly, although the amount of unionized fentanyl varies with pH, the maximum solubility of unionized fentanyl does not vary with pH. D.I. 150 at 831:1-832:4. Thus, if pH is too high, an excess of unionized fentanyl will form and precipitate out of solution. D.I. 150 at 828:1-830:21.

At the optimum pH at which the concentration of unionized fentanyl in solution is maximized,[43] a large proportion of the fentanyl in solution will also be in the ionized form. D.I. 150 at 832:22-834:14. This is important because as a molecule of unionized fentanyl is absorbed through the buccal membrane, a molecule of ionized fentanyl will instantaneously convert to the unionized form to replace the molecule that has just been absorbed.[44] *Id.* Thus, the ionized fentanyl acts as a reservoir to replenish the unionized fentanyl that has been absorbed across the buccal mucosa. *Id.* In this way, the concentration of unionized fentanyl in solution remains at its maximum level, and according to Fick's law[45], the rate of fentanyl absorption is maximized.[46] D.I. 150 at 828:1-831:6, 832:22-834:14.

As Dr. Illum admits, the Henderson-Hasselbalch equation can be used to calculate the optimum pH for fentanyl absorption.[47] D.I. 149 at 656:5-657:15, 659:9-24. Because the concept of an optimum pH describes a particular pH value, it is clear that the optimum pH is a steady pH, and not a dynamic pH. D.I. 150 at 823:12-14. For example, if the pH of a solution is too low, too much

[43] The maximum amount of unionized fentanyl that can be in solution is approximately 10 micrograms per milliliter. D.I. 150 at 831:1-831:21.
[44] Dr. Illum agrees that the conversion from the ionized form of fentanyl to the unionized form is instantaneous. D.I. 149 at 656:24-657:4.
[45] Fick's law states that absorption is proportional to the concentration of a molecule (*e.g.*, soluble, unionized fentanyl). D.I. 150 at 828:1-829:7, 832:22-833:19.
[46] Dr. Illum admits that for maximum fentanyl absorption the concentration of unionized fentanyl in solution should be at the maximum concentration without any precipitation of the unionized fentanyl out of solution. D.I. 149 at 660:16-23.
[47] The concept of an optimum pH describes an ideal situation. D.I. 150 at 839:17-840:8. Due to real world delivery and formulation considerations, practically speaking it is more appropriate to think of an optimum pH as a narrow range. *Id.*

fentanyl will be in the ionized form rather than in the absorbable unionized form. D.I. 150 at 828:1-829:20. Thus, according to Fick's law, the rate of fentanyl absorption will be low at a low pH. *Id.* Similarly, if the pH of a solution is too high the concentration of unionized fentanyl will exceed its solubility, and the excess unionized fentanyl will precipitate out of solution. D.I. 150 at 828:1-830:21. Precipitated fentanyl cannot be absorbed and thus, the rate of fentanyl absorption will decrease.[48] *Id.*

It was well known in the prior art that excipients can be included in a dosage form to adjust saliva pH to the optimum pH range. D.I. 150 at 825:23-827:8; DTX 412 at col. 13, ll. 45-47. In fact, as Dr. Illum acknowledged, Plaintiffs stated in their NDA that sodium carbonate was included in the Fentora® tablet to serve this function. D.I. 149 at 645:10-647:22; PTX 259 at CEP-FEN00029795-796. Similarly, the Mylan ANDA product utilizes an excess of sodium carbonate base to reach, and maintain, the optimum pH range. D.I. 148 at 448:14-449:7, 482:21-483:22.

b. Plaintiffs Commissioned Two Studies to Determine the Effect of Effervescence on Drug Absorption that They Now Try to Discredit

(i) <u>The Absorption Systems Study Demonstrates Effervescence Does Not Increase Fentanyl Absorption through the Buccal Mucosa</u>

Plaintiffs commissioned Absorption Systems, an independent lab, to conduct a study that evaluated the effect of several formulations on the *in vitro* permeation of fentanyl through a buccal membrane. D.I. 150 at 861:5-15; DTX 56; DTX 57. The evaluation was "undertaken to understand the interaction of effervescence and pH modifying agents on the enhancement of buccal permeability of fentanyl." DTX 57 at CEP-FEN01146446. Accordingly, the formulations tested

[48] In contrast to the instantaneous conversion from the ionized form to the soluble, unionized form, the conversion from the solid, precipitated form to the soluble, unionized form of fentanyl is very slow. D.I. 150 at 834:15-836:1.

differed based on the presence or absence of various effervescent agents, *i.e.*, citric acid, sodium bicarbonate, and sodium carbonate. *Id.*; D.I. 150 at 861:5-15.

The formulations tested by Absorption Systems are summarized in the following table: [49]

Terminology and Composition of Formulations Tested

	Effervescence	½ Effervescence	No Sodium Carbonate	Non-effervescent	Citric Acid Only	Sodium Carbonate Only
Fentanyl Citrate	1.256 mg	1.256 mg	1.256 mg	1.256 mg	1.256 mg	1.256 mg
Mannitol	95.744 mg	141.744 mg	115.744 mg	187.744 mg	157.744 mg	167.744 mg
Sodium Starch Glycolate	6.000 mg	6.000 mg	6.000 mg	6.000 mg	6.000 mg	6.000 mg
Sodium Bicarbonate	42.00 mg	21.00 mg	42.00 mg	0.000 mg	0.000 mg	0.000 mg
Citric Acid	30.00 mg	15.00 mg	30.00 mg	0.000 mg	30.00 mg	0.000 mg
Sodium Carbonate	20.00 mg	10.00 mg	0.000 mg	0.000 mg	0.000 mg	20.00 mg
Magnesium Stearate	4.000 mg	4.000 mg	4.000 mg	4.000 mg	4.000 mg	4.000 mg
Pigment	1.000 mg	1.000 mg	1.000 mg	1.000 mg	1.000 mg	1.000 mg

(Admitted as DDX 0004; *See* D.I. 149 at 664:25-666:21). As shown in the above table, the formulations labeled "Effervescence" and "1/2 Effervescence" contained both agents to create effervescence (citric acid and sodium bicarbonate), and a pH-adjusting substance (sodium carbonate). D.I. 150 at 864:16-19; DTX 57 at CEP-FEN01146469.

The third effervescent formulation tested by Absorption Systems labeled "No Sodium Carbonate" above contained citric acid and sodium bicarbonate, but not sodium carbonate (the pH-adjusting substance). D.I. 150 at 864:20-865:13; DTX 57 at CEP-FEN01146469. The authors of the Agarwal manuscript specifically described the purpose of this formulation was "to evaluate the

[49] The formulation of each tablet tested is listed in a draft manuscript ("the Agarwal manuscript") that reports and discusses the results of the Absorption Systems study. D.I. 150 at 862:16-25; DTX 57 at CEP-FEN01146469 (Table 1). There is a typo in Table 1 of DTX 57, and the column labeled "Sodium Carbonate Only" should have an "x" in the sodium carbonate box instead of the sodium bicarbonate box. D.I. 150 at 863:4-864:5.

effect of ingredients that cause liberation of carbon dioxide in the absence of a pH modification agent." D.I. 869:13-870:3; DTX 57 at CEP-FEN01146448.

Absorption Systems also evaluated two formulations without any effervescent agents as experimental controls. A non-effervescent tablet formulation labeled "Noneffervescent" did not contain any effervescent agent or pH-adjusting substance. DTX 57 at CEP-FEN01146447,-4649. An additional experimental control evaluated the permeability of fentanyl citrate dissolved in a buffer solution with a pH of 7. D.I. 150 at 865:14-866:16; DTX 57 at CEP-FEN01146469.

The permeability of the effervescent formulation labeled "No Sodium Carbonate," is not statistically different from the two control formulations, *i.e.*, the non-formulated fentanyl in solution and the non-effervescent formulation. D.I. 150 at 865:14-867:6. Accordingly, the results of the Absorption Systems experiment shows that effervescence by itself, *i.e.*, a formulation that contains only citric acid and sodium bicarbonate, without an excess of sodium carbonate base, does not enhance the permeation of fentanyl through a buccal membrane. *Id.*; DTX 56 at CEP-FEN00471819. It is only when the basic sodium carbonate pH-adjusting substance is added to an effervescent formulation that an increase in permeation is observed. D.I. 150 at 861:16-862:15, 864:16-19; DTX 56 at CEP-FEN00471819. Moreover, if effervescence were truly having an effect on absorption, then one would expect the No Sodium Carbonate formulation to have twice the permeability of the Half-Effervescent formulation because it has twice the amount of effervescence, *i.e.*, twice as much citric acid and sodium bicarbonate. But it does not. DTX 56 at CEP-FEN00471819 (Compare Treatments 4 and 7). Accordingly, the Absorption Systems study demonstrates that if a formulation has good disintegration and agents that adjust the pH within the optimum range, then the best absorption can be achieved. D.I. 150 at 870:4-13.

The Agarwal manuscript also includes a figure correlating pH with the permeability coefficients obtained from the Absorption Systems study. D.I. 150 at 867:7-19; DTX 57 at CEP-

FEN01146467. The figure shows the pronounced effect that pH has on fentanyl permeability through the buccal mucosa. D.I. 150 at 867:7-868:18. For example, the formulation labeled "SC only" contains only sodium carbonate, and has a pH of 10.0. *Id.*; DTX 57 at CEP-FEN01146467,-469. However, the permeability for this formulation is very low because the pH is so high that a large amount of the fentanyl has precipitated out of solution and therefore cannot be absorbed through the membrane. D.I. 150 at 867:7-868:18. Similarly, the formulation labeled "CA" contains only citric acid, and has a pH of 2.2. DTX 57 at CEP-FEN01146467, -469. The permeability for this formulation is very low, because the pH is so low that too much fentanyl is in the ionized form and not enough is in the soluble, unionized form. D.I. 150 at 828:1-829:20.

The figure also shows that the tablet labeled "No Sodium Carbonate" has a pH of 6.0, and has a lower permeation when compared to the tablet labeled "Effervescent," which has a pH of 6.4. D.I. 150 at 868:19-869:12; DTX 57 at CEP-FEN01146467. The reason is at a pH of 6.4 the amount of unionized fentanyl in solution was near the maximum concentration of ten micrograms per milliliter, whereas at a pH of 6.0 the amount of unionized fentanyl in solution was too low.[50] *Id.* The tablet labeled "Half Effervescent" with a pH of 6.8 had a lower permeation than the tablet labeled "Effervescent" because at a pH of 6.8 the amount of fentanyl in the unionized form exceeds its solubility, therefore some of it precipitates as the solid, non-absorbable form. *Id.* In sum, the figure shows significant absorption at a pH range of 6.4-6.8, with the highest permeability at a pH of 6.4. *Id.* Thus, the Absorption Systems experiments confirm Dr. Weiner's testimony that the best fentanyl absorption is achieved at the optimum pH and effervescence or dynamic pH shifts are not involved.

[50] Calculating the amount of unionized fentanyl present at a given pH can be easily done through the use of the Henderson-Hasselebalch equation. D.I. 150 at 868:19-869:12. Dr. Illum agrees. D.I. 149 at 659:9-24.

Plaintiffs criticize the Absorption Systems experiments by arguing that the absorption during the first five minutes of the experiment was not considered. D.I. 153 at 43. This criticism is misplaced, because the first data point taken, *i.e.*, time point zero, actually takes into account the permeation that occurred during the first 5 minutes.[51] D.I. 150 at 870:14-871:17. Evidence that the Absorption Systems study takes into account what happens in the first 5 minutes is shown in Appendix B of the study report, which includes a measurement of the cumulative receiver concentration over time for all of the formulations tested. DTX 56 at CEP-FEN00471826-829 (Appendix B). The formulations labeled "Effervescent" and "No Sodium Carbonate" show a concentration at time zero which proves that Absorption Systems study takes into account the fentanyl that permeates in the first five minutes before the first time point is taken. D.I. 150 at 991:1-993:9; DTX 56 at CEP-FEN00471826, -828.

In support of this criticism, Dr. Illum asserted at trial that the time zero point would not measure the rate of permeability that takes place in the first minute or less when the so-called "dynamic pH" is supposedly occurring.[52] D.I. 149 at 710:9-713:17. According to Dr. Illum, the rate of permeation would be very high in this first minute. *Id.* But Dr. Illum is mistaken and contradicts her own testimony. D.I. 150 at 873:20-875:2; D.I. 149 at 619:3-6. The rate of permeation in the first minute would be expected to be low because the pH value is around 4 during that first minute which means there is very little unionized fentanyl in solution. *Id.* Dr. Illum admits that when the pH is low then absorption of fentanyl is not enhanced. D.I. 149 at 619:3-6. In

[51] The apparent permeability value calculated in the Absorption Systems study takes into account the cumulative fentanyl absorbed, and the time zero point includes the permeation that occurred during the 5 minutes for tablet disintegration and solution mixing. D.I. 150 at 871:11-873:14.
[52] In making her criticism, Dr. Illum made reference to a microenvironment pH profile, and points to the change in pH observed in the first minute. D.I. 149 at 710:9-713:17; DTX 57 at CEP-FEN01146466. However, the microenvironment pH profile that Dr. Illum points to is a measurement of pH over time, and not a measure of concentration versus time. D.I. 150 at 874:10-23. Dr. Illum even admits this. D.I. 149 at 673:7-15.

contrast, the rate of permeability would be expected to be much higher at the higher pH values, because more of the fentanyl is in the unionized form. D.I. 150 at 874:10-875:11.

Curiously, and despite their criticisms, Plaintiffs argue that the Absorption Systems study actually supports their theory that effervescence increases absorption. D.I. 153 at 42-44. Once again, Plaintiffs ignore the clear data of their own studies to reach this conclusion. The Absorption Systems study contains the clearest point measuring the effect of effervescence in isolation from the contribution of a pH adjusting substance, *i.e.*, the "No Sodium Carbonate" formulation. The "No Sodium Carbonate" formulation clearly shows that effervescence in isolation from a pH adjusting substance does not affect, much less increase, the permeability of fentanyl across the buccal mucosa. D.I. 150 at 865:14-867:6, 869:20-870:36.

Plaintiffs argue that tablets with citric acid, sodium bicarbonate, and sodium carbonate had better absorption than tablets that contained sodium carbonate alone, and thus effervescence and pH adjuster is better than pH adjuster alone. D.I. 153 at 43. Plaintiffs again fail to fairly consider the evidence presented at trial. The "Sodium Carbonate Only" formulation had a pH of 10 which means the vast majority of the fentanyl would have precipitated out of solution and thus be unavailable for absorption. D.I. 150 at 867:20-868:18. In contrast, the formulations containing citric acid, sodium bicarbonate, and sodium carbonate have a pH near the optimum, at which little or no unionized fentanyl has precipitated out of solution. D.I. 150 at 868:19-869:12. Moreover, the Agarwal manuscript notes that the "Sodium Carbonate Only" tablet did not completely disintegrate during the assay period.[53] DTX 57 at CEP-FEN01146450.

Plaintiffs also argue that the tablets showing the receiver concentration of the various formulations at various time points prove that effervescence enhances absorption in the first five

[53] Because the "Sodium Carbonate Only" formulation does not completely disintegrate, the formulation also demonstrates that, contrary to Plaintiffs' position, simply having sodium starch glycolate in a formulation is not sufficient to disintegrate the tablet. D.I. 153 at 44-47.

minutes of the Absorption Systems experiment.[54] D.I. 153 at 44. As an initial matter, this argument is in conflict with Plaintiffs' argument that the Absorption Systems permeability results do not take into account the effect of effervescence in the first 5 minutes. *Id*. at 42-43. Nevertheless, the receiver concentration tables do not prove that effervescence enhances absorption; rather, the tables prove that rapid tablet disintegration in combination with pH adjustment are essential for fentanyl permeability across the buccal membrane. D.I. 150 at 991:6-993:1.

The formulations labeled "Effervescent" and "No Sodium Carbonate" show a receiver concentration at time zero, but the other formulations tested do not. D.I. 150 at 991:1-993:9; DTX 56 at CEP-FEN00471826-829. The reason for this is that these two formulations contained the full amount of effervescence, and thus were able to disintegrate more rapidly than the other formulations tested. D.I. 150 at 972:13-20; 992:10-993:1. Notably, the formulation labeled "Half-Effervescent" did not show any fentanyl concentration at time zero. D.I. 150 at 972:10-12; DTX 56 at CEP-FEN00471829. The control formulation that consisted of only fentanyl citrate in solution also did not show any fentanyl concentration at time zero. D.I. 150 at 993:2-6. However, the pH of the fentanyl in solution was at a pH of 7.0, and so one would expect to see some fentanyl precipitate out at that pH. D.I. 150 at 993:2-15. Accordingly, the Absorption Systems cumulative receiver concentration tables also emphasize the importance of rapid disintegration combined with pH control in the absorption of fentanyl across the oral mucosa.[55]

[54] Plaintiffs argue that Dr. Weiner did not look at the receiver concentration tables. D.I. 153 at 44. In fact, he testified extensively about those tables. D.I. 150 at 967:21-968:3, 991:2-993:15.

[55] The formulation labeled "Effervescent" had a greater concentration in the receiver chamber than the formulation labeled "No Sodium Carbonate" at time zero. *Compare* DTX 56 CEP-FEN00471826 with DTX 56 at CEP-FEN00471828. The "Effervescent" formulation also contained a pH-adjusting substance and the most favorable pH for absorption. This further underscores the importance of pH control in fentanyl absorption through a buccal membrane.

(ii) The Anesta Dog Study Does Not Prove that Effervescence Enhances Fentanyl Absorption

In an attempt to prove their hypothesis that effervescence increased the absorption of fentanyl through the buccal mucosa, Plaintiffs commissioned a study by Anesta. D.I. 150 at 875:12-21; DTX 397. The stated purpose of the Anesta study was "to evaluate the effect of effervescence on the enhancement of fentanyl absorption through the oral mucosa." D.I. 150 at 876:16-19; DTX 397 at CEP-FEN00395020. That is the very question that is before this Court. The answer to that question was that "the data in this study do not support the hypothesis that effervescence enhances fentanyl absorption through the buccal mucosa, as pH was not constant during the administration of the fentanyl tablets." D.I. 150 at 882:25-883:19; CEP-FEN00395020.

The Anesta study involved the testing of two effervescent tablet formulations, two non-effervescent tablet formulations, and two fentanyl solution formulations. D.I. 150 at 876:20-878:2; DTX 397 at CEP-FEN00395020. The fentanyl solutions had a pH of 7.0 and 8.05[56]. *Id.* The tablet formulations tested in the Anesta study are summarized in the following table:

Anesta Formulations

Component Number	Component Name	LB462-20: SDNE Quantity (mg/tab)	LB462-25: SDE Quantity (mg/tab)	LB462-30: LDNE Quantity (mg/tab)	LB462-35: LDE Quantity (mg/tab)
RD-04632-20	Fentanyl Citrate, USP	1.57	1.57	1.57	1.57
RD-12132-20	Lactose Monohydrate, NF, 316 Fast Flo	232.97	119.47	480.93	270.93
RD-09120-20	Microcrystalline Cellulose Silicified, NF	232.97	119.47		
RD-22726-20	Sodium Carbonate, Anhydrous		46.99		40.00
20-02018-900	Sodium Bicarbonate, No.1 USP		105.00		105.00
20-03113-900	Citric Acid, Anhydrous Fine Granular USP		75.00		75.00
20-09203-900	Crospovidone, NF	24.99	25.00	10.00	
20-04820-900	Magnesium Stearate, NF	5.00	5.00	5.00	5.00
20-09126-900	Colloidal Silicon Dioxide, NF	2.50	2.50	2.50	2.50
	TOTAL	500.00	500.00	500.00	500.00

[56] The solution with a pH of 8.05 was intended to have a pH of 8.4, and is actually referred to as Soln. 8.4 in the Anesta report. DTX 397 at CEP-FEN00395029.

(Admitted as DDX 0215; *See* D.I. 150 at 879:15-880:10). The effervescent formulations tested in the Anesta study (labeled SDE and LDE in the above table) contained not only effervescent components (citric acid and sodium bicarbonate), but also the pH-modifying agent (sodium carbonate). D.I. 150 at 878:5-880:25. The non-effervescent tablets (labeled SDNE and LDNE in the above table), contained neither the effervescent component nor the pH-adjusting substance. *Id.* So, once again, when Plaintiffs refer to an effervescent formulation they refer to a formulation that includes both the effervescent agents and the pH-adjusting substance.

During the administration of these formulations, the Anesta authors observed that saliva pH changed significantly during administration.[57] DTX 397 at CEP-FEN00395027. As a result of this observation, the Anesta authors made a decision to dose all subjects with a control solution to mimic the pH increase. *Id*. They accomplished this by titrating with the pH 8.4 solution such the pH increased from 7 to a final pH similar to that of the effervescent tablets. *Id.* The Anesta authors were keenly aware of the importance of saliva pH in the absorption of fentanyl through the oral mucosa. DTX 397 at CEP-FEN00395031 (citing a paper by Streisand et al.,[58] entitled "Buccal absorption of fentanyl is pH-dependent in dogs."). The results of the Anesta study confirm the findings of Streisand, and correlate pharmacokinetic values with pH. D.I. 150 at 881:1-882:21; DTX 397 at CEP-FEN00395037-038 (Figures 2-4).

To better illustrate their pharmacokinetic results, the Anesta authors generated several figures. Figure 2 of the Anesta study charts Cmax as a function of saliva pH. DTX 397 at CEP-FEN00395037. In the Figure legend, the authors note that "fentanyl Cmax is strongly dependent on pH…" D.I. 150 at 881:1-882:21; DTX 397 at CEP-FEN00395037. Figure 3 of the Anesta study

[57] As discussed above in Section IV(B)(1)(d)(ii), pH increases as the basic components in the tablets dissolve. There is no evidence that the increase in pH is attributable to effervescence.
[58] Dr. Illum also admits that Streisand et al. correlated the absorption of fentanyl through the buccal mucosa with pH. D.I. 149 at 639:16-22.

charts AUC as a function of the final saliva pH (the charts only show the final pH's, not the range of pH's over time). DTX 397 at CEP-FEN00395037. In the Figure legend for Figure 3, the Anesta authors again concluded "[s]aliva pH also significantly effects [sic] the AUC of fentanyl administered by the oral transmucosal route." D.I. 150 at 881:1-882:21; DTX 397 at CEP-FEN00395037. The Anesta authors further concluded that "[e]ffervescence does not appear to significantly effect [sic] AUC." *Id.* Thus, the Anesta authors introduced the report with their conclusions that "[d]ifferences in pharmacokinetic parameters observed among the formulations tested in this study are most likely due to differences in pH of the formulations." D.I. 150 at 882:25-883:19; DTX 397 at CEP-FEN00395020.

Accordingly, the Anesta data does not prove that effervescence enhances absorption of fentanyl through the oral mucosa, and in fact suggests (correctly) that the absorption is dependent on pH. *Id.* At the very least, the Anesta study does not prove effervescence enhances absorption. *Id.*

c. Plaintiffs Mischaracterize the Mylan Development Work

Throughout its Opening Brief, Cephalon mischaracterizes Mylan's development work by persistently ignoring the fact that when Mylan referred to effervescent formulations, it included formulations containing both the agents for creating effervescence and the pH adjusting substance.[59] D.I. 150 at 855:25-856:19; D.I. 148 at 431:3-8; 448:14-449:7; DTX 680 at MYLAN 518090. When placed in the proper context, *i.e.* taking into account the effects of both the effervescence (from the sodium bicarbonate and the citric acid) as well as the separate pH adjusting substance (sodium carbonate), the results of all of the studies performed as part of Mylan's development work are

[59] For example, in describing the effervescent couple in their formulations, Mylan notes that all three effervescent batches contain 46% weight by weight of effervescent couple. D.I. 150 at 856:20-857:2. However, to reach 46% weight by weight one has to add the citric acid, sodium bicarbonate, and sodium carbonate together. D.I. 150 at 857:3-16.

entirely consistent with Dr. Weiner's explanation that the drug absorption seen in Mylan's ANDA product is due to optimizing saliva pH by incorporating a base (sodium carbonate) that raises pH and maximizes the amount of unionized fentanyl in solution. Nothing in the Mylan development data provides any evidence that effervescence is doing anything beyond speeding the disintegration of Mylan's tablet. D.I. 150 at 840:13-18.

The contents of the test formulations that Mylan scaled up and tested are summarized above in Section III(D) and are not be repeated here. As explained above, Mylan developmental data for Lot 306 demonstrates effervescence does not cause a dynamic pH. *See* Section IV(B)(1)(d)(ii) at 32-33. Mylan's developmental data for Lots 367 and 368 demonstrates that the presence of up to 5% sodium starch-glycolate, a super-disintegrant, is not sufficient to disintegrate the Mylan ANDA product within the required time, as Plaintiffs erroneously assert. D.I. 150 at 855:1-9. *See* Section IV(B)(2)(b), (c) above. Additionally, all three of Mylan's effervescent formulations disintegrated rapidly, and contained a separate pH adjusting substance (sodium carbonate) as well as effervescent agents (citric acid and sodium bicarbonate). DTX 680 at MYLAN 518090, 518160. Accordingly, Mylan's effervescent formulation developmental efforts demonstrate that a formulation that rapidly disintegrates, and contains ingredients that adjust saliva pH to an optimal range as quickly as possible will deliver increased amounts of fentanyl across the oral mucosa when compared to formulations that do not have those characteristics. D.I. 150 at 857:17-858:1.

After the ANDA at issue in this case had been filed, Mylan also conducted some development work on a different fentanyl sublingual product, a generic version of Abstral®. D.I. 148 at 435:16-18. During development of the sublingual product, the lead formulator on the sublingual project, Dr. Danny Kuntz, reviewed the work that was done by others on the fentanyl buccal tablet project and prepared a presentation summarizing his interpretation of the fentanyl buccal tablet development. DTX 680. One of the slides prepared by Dr. Kuntz, and reproduced in

Plaintiffs' brief, contains statements describing the Plaintiffs' "dynamic pH" theory. DTX 680 at MYLAN 518094. Plaintiffs attempt to characterize this slide as an "admission" that Mylan "believed" the "dynamic pH" theory prior to trial.[60] D.I. 153 at 28-30. However, the fact that Dr. Kuntz copied information originating in Dr. Pather's 2008 paper into a presentation, does not mean that Dr. Kuntz -- much less Mylan – "believed" the unproven "dynamic pH" hypothesis. Dr. Kuntz did not admit that those theories were valid, nor did Mylan. D.I. 150 at 858:11-22. As Dr. Wargo testified, Mylan did no independent evaluation of the Pather theories.[61] They were included in the report as information from published literature. In fact, Dr. Twist, the senior formulator on the fentanyl buccal tablet project testified that even after the project was completed, knowing everything he knows today, he was "skeptical" that effervescence actually improves absorption of fentanyl across the oral mucosa. D.I. 148 at 515:2-516:4.

d. The Plaintiffs' Clinical Study Fails to Show That Effervescence Has Any Effect on Absorption

Plaintiffs conducted a pharmacokinetic study 099-06 ("the Ireland study") that compared an effervescent tablet, a non-effervescent tablet, and Actiq®. D.I. 150 at 883:20-884:24; D.I. 149 at 553:24-554:20. As in the Mylan pharmacokinetic studies, the Anesta dog study and the Absorption Systems study, when the investigators in the Ireland study referred to "effervescent" formulations, those formulations included both the effervescent agents and the pH adjusting substance. The effervescent tablet contained citric acid, sodium bicarbonate, and sodium carbonate whereas the

[60] Plaintiffs also cite to other statements from Dr. Kuntz' presentation on the fentanyl sublingual project (*e.g.* "effervescence has a larger effect on PK than other pH modifiers" and "pH modification alone and effervescence are not equivalent.") that they also mischaracterize as admissions from Mylan about the effect of effervescence. D.I. 153 at 28, citing DTX 680 at MYLAN 518091. Again, however, Plaintiffs ignore the fact that Dr. Kuntz' use of the term "effervescence" also includes the contribution of the pH-adjusting substance. D.I. 150 at 855:25-856:19, 859:4-860:6; D.I. 148 at 431:3-8; 448:14-449:7; DTX 680 at MYLAN 518090.

[61] Dr. Wargo confirmed that Mylan did not independently test the scientific principles reported in the Pather paper to see if they were accurate, and that Mylan's formulators, including Dr. Kuntz, just "regurgitated" the theory from the published literature. D.I. 148 at 457:2-7, 507:12–24.

non-effervescent tablet did not contain any of those components.[62] D.I. 150 at 884:25-886:16; DTX 541 at CEP-FEN00150997-998. Because Plaintiffs failed to account for the impact of the basic pH adjusting substance on absorption, the Ireland study does not demonstrate that effervescence increases absorption across the oral mucosa. D.I. 150 at 886:17-887:8. Just as in the Anesta study, the pharmacokinetic results obtained in the Ireland study can be explained by the well-known effect of pH on fentanyl absorption. *Id.*; D.I. 150 at 881:1-883:19.

Plaintiffs argue that the disintegration times of the non-effervescent and effervescent formulations tested in the Ireland study were similar, and thus the disintegration rate did not contribute to absorption differences between the formulations. D.I. 153 at 36. Plaintiffs' only support for this argument is a reference to an article describing the results of the Ireland study that cryptically states that the disintegration times were similar "as tested by a specially developed method for buccal tablets." *Id.*, *citing* PTX 266 at CEP-FEN00672928. But the paper gives no details as to the results of the method or how the "specially developed method" was conducted. D.I. 150 at 987:15-988:19; PTX 266. Importantly the paper does not report any actual disintegration times or rates, *i.e.*, whether the effervescent formulations disintegrate faster than the non-effervescent formulations. PTX 266. Accordingly, the article on which Plaintiffs rely contains only a bare assertion that the disintegration times are similar with no information that would allow the Court to assess the reliability of the method, the time periods over which disintegration was measured or the relative rates of disintegration.

Plaintiffs also attempted to elicit testimony at trial that the pH's of solutions of the non-effervescent and effervescent formulations were similar, to support an argument that absorption difference cannot be attributed to differences in pH. D.I. 153 at 36-37. However, this argument

[62] So, again, when Plaintiffs refer to an effervescent tablet they are actually referring to a tablet that includes a pH-adjusting substance as well as the effervescent agents, just as does Mylan.

collapsed when Mylan's witness described the *in vitro* pH tests that were used to generate the values upon which Plaintiffs attempted to rely.

At trial, Dr. Illum asserted on cross examination that the pH values for the effervescent and non-effervescent formulations tested in the Ireland study were nearly identical. D.I. 149 at 695:25-698:16. As if intending to spring a trap, for the first time on redirect examination Plaintiffs introduced a document to which Dr. Illum did not refer on direct examination, that had not been mentioned in Dr. Illum's expert reports or her deposition, and had not been disclosed to Defendants in advance of her testimony in accordance with the Court's procedures. D.I. 150 at 891:5-892:2. In addition, the exhibit cited by Dr. Illum does not give any information about how the pH measurements were made, the identity or volume of the solution in which the tablets were dissolved to measure pH. D.I. 150 at 889:9-21; PTX 438. Even Dr. Illum admitted that she did not know how the *in vitro* pH measurements were made. D.I. 149 at 651:19-652:14. Dr. Illum also admitted that she did not know what the *in vivo* pH profile of the non-effervescent and effervescent formulations would look like. D.I. 149 at 653:1-4. Accordingly, no conclusions regarding the significance of the pH values reported in PTX 438 could be made. D.I. 150 at 889:22-890:8.

Despite not having prior notice of Plaintiffs' "evidence," Dr. Weiner was able to identify the methodology that Plaintiffs used to obtain the pH values presented by Dr. Illum.[63] D.I. 150 at 892:3-19. The pH values were obtained through the use of a CIMA protocol referred to as ATM-360. D.I. 150 at 892:15-896:3; DTX 765A-C; DTX 766A-D. ATM-360 states that five milliliters of a pH 7.0 buffer was used to dissolve both the effervescent and non-effervescent tablets. D.I. 150 at 898:23-900:15; DTX 21 at CEP-FEN00965582-83. Importantly, a buffer is a solution that resists

[63] Dr. Weiner identified several analysis sheets that reported testing the pH of the effervescent and non-effervescent lots tested in the Ireland study. D.I. 150 at 892:15-896:3; DTX 765A-C; DTX 766A-D. Importantly, in every case the pH that resulted from the *in vitro* test was around 7.0. D.I. 150 at 896:12-898:16; DTX 765A-C; DTX 766A-D.

changes in pH that would normally accompany the addition of an acid or a base to the solution. D.I. 150 at 900:6-10. Five milliliters is simply too much buffer to use in evaluating the pH of a tablet intended to be placed in the buccal cavity. D.I. 150 at 900:24-901:13. Because so much of a pH 7.0 buffer was used in these pH tests, it is not surprising that the pH of the effervescent and non-effervescent tablets both measured about 7. D.I. 150 at 900:16-23. In effect, all that is being tested is the pH of the buffer. *Id.* The Cima scientists recognized this problem and subsequently modified the protocol to use a much smaller volume of buffer. D.I. 150 at 901:14-903:7; DTX 21 at CEP-FEN00965578-579. Accordingly, there is absolutely no evidence that the *in vitro* pH profiles of the effervescent and non-effervescent tablets evaluated in the Ireland study were similar. Because the effervescent formulation in the Ireland study indisputably contained an excess of the basic sodium carbonate pH adjusting substance, and the non-effervescent formulation did not, it defies logic that they would produce the same pH's. In fact, the pH profiles of the Anesta tablets, which had similar formulations to the tablets in the Ireland study, show just the opposite.

The Ireland study results are entirely consistent with Dr. Weiner's explanation that rapid tablet disintegration and pH modification are the key factors for the effective delivery of fentanyl across the oral mucosa. The differences in rates of absorption between the non-effervescent and the effervescent formulations tested in the Ireland study can be explained by the known effect of saliva pH on fentanyl absorption, as in the Anesta study.

C. Cephalon Has Not Met Its Burden of Proving That Mylan's ANDA Product Infringes the Asserted Claims of the '158 Patent

Until just before trial, Cephalon asserted that Mylan infringed four patents belonging to the same family of patents (the "Moe patents"). At trial, Cephalon narrowed its allegations to assert only the '832 and '158 patents, which share the same specification. *See* JTX6 and JTX8. That specification describes both pH adjusting substances such as carbonates that <u>are</u> effervescent

materials and other pH adjusting substances such as phosphates that are not effervescent materials. *See* D.I. 150 1011:19-1012:4; JTX 6, col. 27, ll. 29-33 ("Preferably, the materials which can be used as pH adjusting substances in accordance with the present invention include carbonates such as sodium, potassium or calcium carbonate or a phosphate such as calcium or sodium phosphate.").

The Moe patents include varying limitations regarding the specific pH adjusting substance claimed. *See, e.g.*, JTX 8, col. 36, ll. 38-43; JTX 6, col. 36, ll. 41-44. Some of the claims, such as in the '832 patent, are directed to dosage forms wherein the pH adjusting substance must be a carbonate. S*ee, e.g.*, JTX 8, col. 36, ll. 38-43. ("a pH adjusting substance comprising a carbonate"). In the '158 patent, in contrast, the patentee narrowed the claims to cover the other disclosed embodiment: the use of non-effervescent pH adjusting substances, such as phosphates. Thus, the claims require that the pH adjusting substance be one that is "not a component of the effervescent material." JTX 6. Having narrowed the claims of the '158 patent to require use of a non-effervescent pH adjusting substance, Cephalon cannot now argue that Mylan's use of an effervescent pH adjusting substance infringes.

There is no dispute that the Mylan ANDA product contains sodium carbonate as the pH adjusting substance. D.I. 149 at 603:3-9. There is also no real dispute that sodium carbonate is an effervescent material. D.I. 149 at 609:24-611:23. The specification of the '158 patent states that the effervescent material typically includes "at least one source of a reactive base, usually a carbonate or bicarbonate." *See* JTX 6, col. 26, ll. 13-14. The '158 patent also recognizes that effervescent material can comprise "sodium carbonate, potassium carbonate, magnesium carbonate and the like." *See* JTX 6, col. 26, ll. 26-27 (emphasis added). Thus, the '158 patent itself teaches that sodium carbonate is a pH adjusting substance that is also an effervescent material.

Expert testimony at trial confirmed what the '158 patent teaches. Dr. Kibbe explained that because "any source of carbonate" will effervesce when in contact with an acid, the sodium

carbonate would be "part of the effervescent activity." D.I. 151 at 1054:16-23. Dr. Illum did not dispute this testimony and in fact agreed that sodium carbonate could participate in the effervescent reaction. D.I. 149 at 611:14-17.

Although Cephalon admits that the sodium carbonate participates in part in effervescent reactions, it asserts that sodium carbonate is still a pH adjusting substance that is not a component of the effervescent material because not all of it is reacts in the effervescent reaction. S*ee* Cephalon Op. Br. at 58-59. Cephalon's position is contrary to the claim language and, indeed, would render superfluous the limitation that the pH adjusting substance is "not a component of the effervescent material" because in all cases pH adjustment occurs only because of those acid or base components that are not involved in the effervescent reaction.[64]

Because the asserted claims of the '158 patent require the use of a pH adjusting substance that is "not a component of the effervescent material" and the pH adjusting substance in Mylan's ANDA product, sodium carbonate, is an effervescent material, Mylan's ANDA product does not infringe the asserted claims of the '158 patent. JTX 6, col. 36, ll. 41-44.

V. CONCLUSION

For at least the foregoing reasons, Mylan respectfully requests that the Court find that Plaintiffs have failed to meet their burden of proving that Mylan's generic fentanyl buccal tablets that are the subject of ANDA No. 202577 infringe or induce infringement of the asserted claims of the '604, '590 and '158 patents. Accordingly, Mylan respectfully requests that this Court enter a judgment of noninfringement in favor of Defendants.

[64] Cephalon incorrectly suggests that there is some inconsistency between Mylan's position with respect to the '832 patent and the '158 patent. Not so. The '832 patent requires that the pH adjusting substance be a carbonate that is not the bicarbonate used to effervesce. What is does not require -- but the '158 patent does -- is that the pH adjusting substance not be an effervescent material.

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Respectfully submitted,

/s/ Elizabeth M. McGeever

Elizabeth M. McGeever (No. 2057)
PRICKETT, JONES & ELLIOTT, P.A.
1310 King Street
P.O. Box 1328
Wilmington, DE 19899
(302) 888-6500

E. Anthony Figg
Sharon L. Davis
C. Nichole Gifford
Seth E. Cockrum
Brett A. Postal
Rachel M. Echols
ROTHWELL FIGG ERNST & MANBECK
607 14th Street, N.W.
Suite 800
Washington, D.C. 20005
(202) 783-6040

Attorneys for Defendants and Counterclaim-Plaintiffs
MYLAN PHARMACEUTICALS INC. and MYLAN INC.